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METABOLISM STUDIES IN CŒLIAC DISEASE

BY

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Since the publication of Cheadle's paper[1] in 1903, the presence of excess of fat in the fæces has attracted much notice as the most characteristic sign of the metabolic disturbance in cœliac disease. It has been recognized that associated with this disturbance of fat absorption, there occurs also a defective retention of minerals and an excessive loss of nitrogen in the fæces. In consequence some attention has been paid to the effect of varying the composition of the dietary, especially from the therapeutic standpoint. The interrelationship of the disturbances in the absorption of the various elements of the diet is a matter of importance both from the practical point of view, and because of the possible value in the explanation of other metabolic disorders. Parsons[2] has already indicated the importance of vitamin D in the prevention of cœliac rickets, showing that the continued absence of this vitamin from the fat-poor diets used in treatment is the cause of the rickets of convalescence. The series of observations detailed in this paper are published in the hope that some further light may be thrown on the underlying chemical pathology of the cœliac state. A more complete understanding of the disorder should ultimately prove of value in the prevention and cure of the disease.

Metabolic studies in cœliac disease are subject to the great disadvantage that sudden changes occur in the condition of the patient although the diet is constant and the environment unaltered. Accordingly it is difficult to determine whether differences in the metabolic findings are to be attributed to changes in food or other treatment, or to natural aggravation or amelioration of the condition. In these investigations as much care as possible was taken to rule out the idiopathic changes in the severity of the disease. A brief description of the salient features of the case-histories of the patients is appended at the end of the paper (see Appendix). It is proposed in the first place to summarize the metabolic findings with regard to the various forms of foodstuffs and thereafter to discuss the bearing of these results on the chemical pathogenesis of cœliac disease.

Utilization of fat (see Table 1).—A characteristic feature of cœliac disease is the presence of a large amount of fat in the fæces which are bulkier than normal. Frequently they are whitish and fatty in appearance, but this depends to a large extent on the intake of fat. It has been stated that there may take place a re-excretion of fat through the intestinal epithelium and

TABLE I.

SHOWING PERCENTAGE AND ABSOLUTE DAILY CONTENT OF FÆCAL FAT WITH PERCENTAGE AND ACTUAL DAILY UTILIZATI

Case No.	Days	Diet*	Dried fæces	% fat in dried fæces	% of fæcal fat			Daily output				Utilization			
													Absorption		
					N.F.	F.F.A.	C.F.A.	N.F.	F.F.A.	C.F.A.	Total fat	Intake	Total	%	per kgrm body wt.
			grm.					grm.	grm.	grm.	grm.	grm.	grm.		
1 (i)	6	N	11·49	32·70	11·6	28·8	59·2	0·43	1·09	2·23	3·77	29·4	25·61	87·2	3
(ii)	6	H	11·99	50·00	13·4	24·8	61·6	0·80	1·48	3·68	5·98	99·2	93·22	94·2	12
(iii)	7	N	15·70	50·94	20·9	40·4	38·6	1·67	3·22	3·09	7·99	24·2	16·21	67·0	2
(iv)	7	H	32·20	57·51	17·0	35·1	47·7	3·17	6·49	8·87	18·53	97·0	78·47	80·9	10
(v)	7	H(a)	16·81	55·74	11·1	31·4	57·4	1·04	2·96	5·40	9·40	97·0	87·6	88·8	10
(vi)	6	N	6·62	44·50	5·6	69·9	24·4	0·15	2·07	0·72	2·94	24·0	21·1	87·6	2
(vii)	6	H	14·79	81·20	2·5	41·6	55·7	0·31	5·05	6·75	12·11	104·3	92·2	88·4	10
(viii)	5	H(b)	11·50	70·20	11·4	35·5	52·4	0·97	2·90	4·27	8·14	104·3	96·2	92·2	10
2 (i)	6	N	12·55	35·60	22·3	54·1	24·0	0·99	2·38	1·08	4·45	34·1	29·6	87·2	3
(ii)	6	H	11·95	38·35	18·2	47·5	36·6	0·83	2·17	1·56	4·56	99·9	95·3	95·4	10
(iii)	7	N	7·99	47·60	11·9	39·0	50·0	0·45	1·46	1·90	3·81	27·1	23·8	86·0	2
(iv)	7	N	12·42	48·00	18·1	65·8	16·0	1·09	3·92	0·96	5·97	35·0	29·0	83·1	3
(v)	7	N	20·10	53·00	13·3	51·4	35·3	1·41	6·91	3·76	12·08	38·4	26·4	68·7	2
(vi)	7	H	17·03	66·80	15·2	41·7	43·1	1·74	4·73	4·90	11·37	75·1	63·7	84·8	6
(vii)	7	H(b)	18·57	64·98	18·2	46·0	35·6	2·20	5·57	4·30	12·07	75·1	63·0	83·9	5
3 (i)	6	N	18·45	40·45	20·9	48·8	30·2	1·58	3·63	2·25	7·46	28·2	20·7	73·6	2
(ii)	6	H	29·77	74·58	20·5	48·6	30·9	3·93	9·37	8·90	22·20	114·7	92·7	80·8	11
(iii)	6	H	39·73	73·95	22·5	53·1	24·4	6·60	15·58	7·17	29·35	126·8	96·4	76·0	12
(iv)	6	H(a)	33·25	69·40	21·6	45·4	32·9	5·00	10·50	7·60	23·10	126·8	103·7	81·8	12
(v)	7	L	19·33	25·98	17·0	49·9	32·6	0·87	2·50	1·64	5·01	8·1	3·1	38·2	0
(vi)	7	N	23·13	49·10	7·2	26·8	65·8	0·83	3·05	7·48	11·36	25·5	14·1	55·3	1
4 (i)	6	N	8·23	26·82	20·3	37·3	42·6	0·45	0·82	0·93	2·21	26·6	24·4	91·0	4
(ii)	7	N	16·73	39·02	15·7	50·3	34·0	1·03	3·30	2·21	6·54	20·5	14·0	68·1	2
(iii)	7	N(c)	13·57	49·01	5·1	19·9	74·9	0·34	1·32	4·99	6·65	17·9	11·3	62·8	2
5 (i)	7	N	28·31	35·03	13·2	72·4	14·4	1·32	7·17	1·42	9·91	34·6	24·7	71·3	3
(ii)	7	N	37·17	44·55	39·4	40·9	19·6	6·50	6·86	3·25	16·61	21·0	4·4	20·9	0
6 (i)	7	N	16·90	58·70	13·6	48·3	38·3	1·33	4·78	3·80	9·91	38·8	28·9	74·4	2
(ii)	6	H	13·14	62·75	13·8	26·5	59·8	1·32	2·55	5·75	9·62	115·0	105·4	91·6	9

*L. Low fat intake.
N. Normal fat intake.
H. High fat intake.

(a) NaH_2PO_4 added.
(b) Sodium glycocholate added.
(c) Radiostol added.

Fanconi[3] gives figures showing an excretion of 28·55 grm. of fat although the intake only amounted to 20·66 grm., thus indicating a re-excretion of almost 8 grm. of fat in the twenty-four hours. Schick and Wagner[4] found a greatly increased percentage of neutral fat, but it is generally agreed the fat-splitting is quite normal. Fanconi describes two types as regards the disturbance in fat absorption, first a group in which the absorption is very poor and where most of the fat is unsplit, and secondly a group in which, despite poor absorption, the splitting is normal.

In our series the neutral fat formed less than one-quarter of the total fæcal fat except in one period in one Case 5 (ii), when the child was obviously going down-hill rapidly. In that period 39·4 per cent. of the total fat was unsplit which could not have been accounted for by increased peristalsis as the daily number of motions was only one or at most two. Otherwise the results of the fæcal analyses indicated excellent fat splitting in most of the cases, and that although the percentage absorption was below normal.

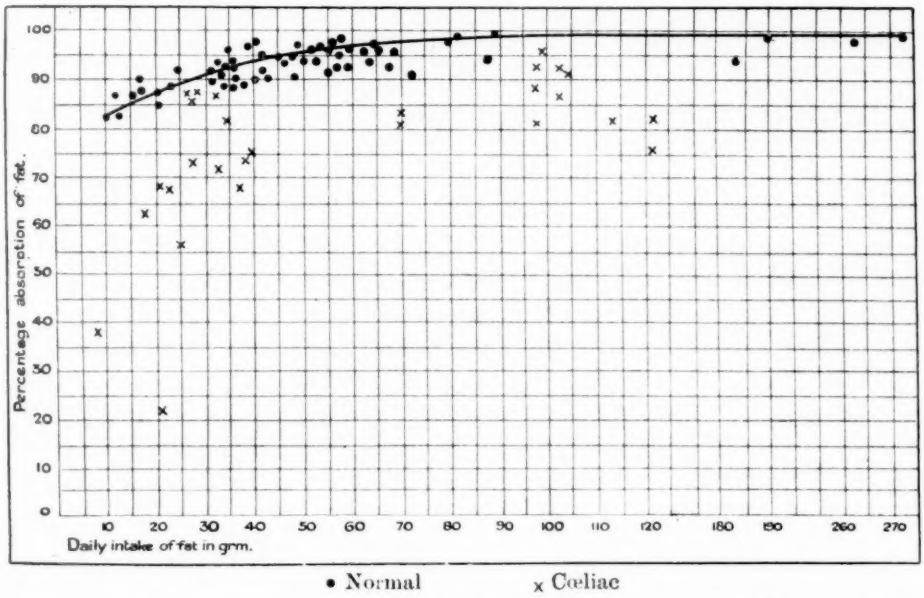

FIG. 1. Showing percentage absorption of fat during different daily intake of fat in health and cœliac disease.

The percentage absorption of fat varied in the individual cases and at different times. Generally it bore a rough relationship to the clinical condition of the patient, provided one kept in mind the actual amount of fat ingested. Harrison and Sheldon[5] state that the finding of a high percentage of total fat in the fæces does not necessarily indicate cœliac disease, but that a normal result in an untreated patient is almost definitely against the diagnosis of cœliac disease. In Case 1 (ii), however, the fat formed half the weight of the dried fæces, whereas in Case 5 (i) only a third, i.e., within normal limits, although the former patient was convalescing rapidly and steadily and the latter was in an acute stage. The percentage absorption was in Case 1 (ii) 94·2 per cent. and in Case 5 (i) 71·3 per cent. It is therefore impossible to

judge of the absorption of fat from a knowledge alone of the percentage composition of the fæces. It is essential to have figures for the fat intake and the weight of the dried fæces so that the percentage absorption of the intake can be calculated.

It has been shown by Hutchison[6] and others that in health the fat forms about one-third of the weight of the dried fæces. Accordingly an increase in the intake of fat will lead to both an absolute and relative increase in its absorption provided the fæces are not excessive in amount. The results charted on Fig. 1 indicate the percentage absorption of fat with varying daily intakes in a series of children, either healthy, or at any rate without gastro-intestinal disorder. If one takes into consideration the varying norm in different individuals the gradual rise in the curve as the intake of fat is increased is all the more striking. When the percentage absorption of fat on varying intakes is estimated in the same individual it is invariably found to increase with the rise in the absolute amount of fat ingested. This held good with a daily intake of some 290 grm. of fat. It is therefore justifiable to conclude that in health the absorptive power of the intestine for fat is practically unlimited, provided, of course that the excess of fat does not lead to intestinal upset.

When the results of the cœliac analyses are examined it is clear that here too the percentage absorption of fat rises with the increase in the daily intake. This can obviously only hold good in the one individual at any particular phase of the cœliac condition owing to the different grades of severity of the disease in different patients and in the same patient at different times. It might be suggested that the lower percentage absorption on the lower fat diet was due to an aggravation of the cœliac state. In all cases, however, the high fat diet followed immediately on the moderate, and everyone is agreed that high fat diet is not beneficial to the cœliac patient. One point of difference between the behaviour of the normal and the cœliac to the increased ingestion of fat is the much greater increase in the weight of the dried fæces in the cœliac patient. Despite this increase in fæcal weight, both the absolute and percentage amounts of fat absorbed were greatly raised. The percentage of total fat in the dried fæces was invariably raised as a result of a higher fat intake. The ratio of neutral to total fæcal fat remained practically unchanged, tending if anything, to be rather lower on the high fat diet. The combined fatty acids (calcium soaps) became appreciably greater in amount both absolutely and relatively to fæcal weight and total fat.

Effect of acid-sodium phosphate.—Administration of di-hydrogen sodium phosphate during a high fat period caused a definite increase in the ratio of insoluble soaps to total fæcal fat and fæcal weight. The percentage absorption was increased quite markedly in both cases. It would seem therefore that this substance promotes conditions favouring fat absorption.

Effect of sodium glycocholate.—The effect was to increase the relative and actual amounts of neutral fat with corresponding diminution in those of the insoluble soaps. The percentage absorption of fat showed a marked increase in one and a slight reduction in the other case. It would appear that glycocholate promotes the absorption of the soaps.

Effect of radiostol.—The percentage absorption of fat was slightly diminished. The absolute amount of combined fatty acids in the fæces was greatly increased as was the ratio of combined fatty acids to total fat A similar effect of vitamin D preparations has been noted in metabolism studies on rickets (MacRae[7]).

The ability of the cœliac patient to deal with fat in the intestine is undoubtedly impaired. During the active stage the percentage absorption is below normal while as a general rule the fat-splitting properties of the intestinal juices are quite up to standard. The defect in fat absorption is much more marked when the intake is low. During a period of high-fat intake the percentage absorption rises usually to a very marked degree. Accordingly the actual amount of fat absorbed during such a period usually exceeds the normal requirements of the child although the percentage absorption is still below the normal figure for that particular daily intake of fat.

It is generally held that administration of fat in large amount immediately produces a recurrence of active symptoms. By this is meant the re-appearance of bulky fatty motions. Two patients, Cases 1 and 2, were given high fat diets for a period of 14 days during a quiescent stage when the fat absorption was about 90 per cent. The fat absorption on the increased fat intake became greater both relatively and absolutely, being quite within normal limits. The motions were practically unchanged in weight and did not present any abnormal appearance. Shortly after this high fat period the patients were discharged without symptoms on a low-fat high-protein diet and remained well for several months only to return with a recurrence of the manifestations of the active disease. It seems justifiable to conclude from this experience that administration of large amounts of fat in a stage of true convalescence does not, for short periods at any rate, lead to recrudescence of symptoms. If, however, the patient is only apparently convalescent, the addition of fat to the diet will lead to the appearance of typical cœliac motions. It is questionable how far the appearance of these fatty stools is indicative of an aggravation of the condition. Even if the percentage absorption of fat were much below normal, fatty stools could not occur when the fat intake was low. Accordingly when such a patient, who has been receiving a minimal amount of fat, ingests more fat, there will appear in the fæces a much greater amount of fatty products than normal, leading to the formation of typical cœliac motions. This gives rise to the impression that the condition has been aggravated although the presence of fatty motions is merely an indication that the intestine is at the time unable to deal properly with fat. Naturally this was not evident on the minimal fat diet as the amount of fat in the food was insufficient to give bulk to the fæces, although the intestinal condition was no better than during the period when the stools were large and fatty.

The varying effects of the administration of acid phosphate, high-fat diet, vitamin D, and sodium glycocholate on the distribution of fat in the fæces are of interest. The first three lead to an increased amount, relatively at any rate, of calcium soaps, whereas glycocholate produces a decrease in the soaps and

presumably an increased absorption of fat in that form. Verzàr and Kúthy[8] maintain that absorption of fats as soaps is impossible unless at a pH of 9 when the soaps are soluble. One of the main functions of the bile salts is to make the soaps soluble at an acid pH which is the normal for the intestine. Klinke[9] also states that calcium soaps are soluble in the presence of bile salts. Adler[27] showed that withdrawal of the bile secretion led to an appearance of calcium soaps which greatly diminished in amount on administration of bile-salts. Our results show that increasing the acidity of the gut by the presence of excess fatty acids, or administration of acid salt or by ingestion of vitamin D raises the proportion of fat found as insoluble soaps. It would therefore seem justifiable to conclude that in these cases the reaction of the intestine is alkaline. The question remains how far this reaction is due simply to the associated vitamin D deficiency which has become secondarily superimposed on the cœliac condition. Sodium glycocholate decreases the absolute and relative amounts of the insoluble soaps. Accordingly it would appear that there is a deficiency in bile salt or at any rate that addition of bile salt is an aid to the absorption of soaps in the cœliac state.

Lime and phosphorus (see Table 2).—The daily retention of lime and phosphorus on a moderate fat-diet, when calculated on the basis of kilogramme of actual weight is either normal or slightly subnormal. The total amount retained, however, is much below that found in the healthy child of the corresponding age, owing to the dwarfism and greatly reduced weight of the cœliac child. Linder and Harris[10] state that the calcium utilization has a rough relationship to the total fat output, being high only when the fat excretion is low. Generally this may be so, but there are numerous exceptions, and it would be unwise to deduce a low calcium retention because of high fat content of the fæces. Thus in Case 2 (vi) there was an average daily excretion of 11·4 grm. fat while the calcium retention was quite good (47 mgrm./kgrm./day), whereas in the previous period when the fat output was practically the same (12·1 grm./days) there was a marked negative retention.

Further evidence that the bulk of fæcal fat cannot be taken as the cause of low calcium retention is obtained from a consideration of the mode of mineral excretion in jaundice. In this condition there is a faulty absorption of fats, the splitting of which is quite normal. The mineral retention is low but while the bulk of the calcium is found in the fæces by far the greater part of the phosphorus is excreted in the urine. The $CaO : P_2O_5$ ratio of the fæces and the urinary P_2O_5 : fæcal P_2O_5 ratio are both abnormally high. This is attributed to the large amount of fatty acid fixing the calcium in the intestine and so liberating much phosphorus to be absorbed and subsequently excreted in the urine.

The results in cœliac disease bear a strong resemblance as far as the mode of mineral excretion is concerned to those seen in rickets where the bulk of the phosphorus is found in the fæces. In rickets, the fat content of the fæces is not raised ; indeed it is during healing that the amount of soaps is relatively and absolutely increased.

EFFECT OF HIGH FAT DIET.—In two experiments this produced a very marked increase in the amount of fæcal calcium. In the third, the fæcal calcium was quite markedly diminished with a consequent rise of the retention of lime. An increased amount of phosphorus was found in the urine in all three cases. This increase in urinary phosphorus cannot be taken as evidence of increased absorption of phosphorus since in the first two experiments (Case 1, iv and vii) the amount found in the fæces was also increased. Only in the third (Case 2, vi), which showed a decrease in fæcal calcium was the phosphorus

TABLE 2.

CALCIUM AND PHOSPHORUS METABOLISM: DAILY INTAKE, OUTPUT AND RETENTION.

Case No.	Days	Diet*	CaO (grm.)					P_2O_5 (grm.)				Urine P_2O_5 / Fæcal P_2O_5 × 100	Fæcal CaO / Fæcal P_2O_5 × 100	Retention grm. per kgrm.	
			Intake	Fæcal output	Fæcal output as soaps	Urinary output	Total retention	Intake	Fæcal output	Urinary output	Total retention			CaO	P_2O_5
1 (iii)	7	N	1·223	1·043	·31	·053	·165	1·791	·972	·421	·399	43·2	103	·022	·055
(iv)	7	H	·973	1·577	·887	·065	−·669	1·495	·998	·562	−·064	56·3	158	−·093	−·009
(v)	7	H(a)	·976	·823	·54	·126	·026	3·007	·756	·967	1·284	128·0	109	·004	·178
(vi)	6	N	1·21	·734	·072	·023	·457	1·81	·913	·361	·542	40·0	80·4	·051	·061
(vii)	6	H	1·15	1·14	·67	·025	−·008	1·79	1·005	·63	·159	62·6	113	−·001	+·018
(viii)	5	H(b)	1·205	·747	·426	·025	·432	1·835	·540	·676	·618	125	138	·045	·066
2 (v)	7	N	1·80	2·31	·375	·037	−·548	2·64	2·090	·368	·181	18	110	−·053	+·017
(vi)	7	H	1·825	1·311	·490	·021	·493	2·25	1·158	1·031	·061	8·9	113	·047	·006
(vii)	7	H(b)	1·775	1·69	·43	·026	·059	2·287	1·43	1·042	−·185	72·8	118	+·005	−·016
4 (i)	6	N	1·287	·650	·093	·031	·606	1·618	·535	·363	·721	68	121	·10	·118
(ii)	7	N	1·48	1·372	·221	·020	·087	2·406	1·606	·311	·489	19	85	·013	·075
(iii)	7	N(c)	1·497	1·085	·499	·026	·385	2·391	·597	1·204	·589	202	181	·060	·094
6 (i)	7	N	1·987	1·673	·378	·022	·292	2·687	1·538	·624	·525	40·6	109	·028	·050
(ii)	6	H	1·890	1·211	·575	·013	·649	2·849	·904	1·10	·845	121	66	·053	·069

*L. Low fat intake.
N. Normal fat intake.
H. High fat intake.
(a) NaH_2PO_4 added.
(b) Sodium glycocholate added.
(c) Radiostol added.

in the fæces diminished. In all three instances the total amount of fæcal fat was increased as was that of insoluble soaps. Accordingly since the increased retention of lime and phosphorus occurring in Case 2 (vi) took place simultaneously with an increase in fæcal fat and soaps, it seems justifiable to argue that the amount of fat in the fæces cannot be more than a secondary factor in hindering the absorption of minerals.

Further, although in Case 1 (iv) and (vii), we find that about 4 grm. extra CaO was fixed as soaps there was no apparent liberation of phosphorus, since

that element was actually increased in amount in the fæces. This is in contrast to the picture met with in jaundice where there is an increased fæcal amount of calcium soaps associated with a diminished fæcal content of phosphorus and an increased excretion of phosphorus in the urine. As already pointed out the increase in urinary phosphorus in these cases has been attributed to an increased intestinal absorption of phosphorus liberated as a result of the increased fixation of calcium as soaps. In cases of cœliac disease on the other hand, there is no evidence of increased absorption of phosphorus as with the increased formation of calcium soaps there is also an increased fæcal phosphorus. It seems fair to conclude, therefore, that the extra urinary phosphorus was not the result of increased absorption.

As regards Case 2 (vi) it might be argued that the increased mineral retention took place during a period of general improvement. That this was not so is indicated by the low percentage absorption of fat for the amount ingested. We have evidence that during this period the carbohydrate metabolism also showed signs of definite impairment. Accordingly it must be admitted that during this period there occurred a marked improvement in the retention of lime and phosphorus, although all the other metabolic findings showed no signs of betterment.

There remains one hypothesis, namely, that the poor retention of minerals is the result of deficiency in vitamin D. Parsons[2] states that the development of rickets in cœliac infantilism is due primarily to the deficient absorption of fat and therefore of vitamin D, calcium and phosphorus. The 'rachitic' mode of mineral excretion is in this connection very suggestive. Further, in agreement with Parsons and other workers, we have found the values for serum calcium and inorganic phosphorus to be low (Table 6). We have studied the effect of vitamin D administration in one case and find that there is a very marked increase of lime and phosphorus retention, and that the main excretory route of phosphorus is shifted from fæces to urine. Further, the percentage absorption of fat is slightly reduced and the weight of fæcal fat is increased, thus affording still more proof that the metabolism of fat and of minerals in cœliac disease are only secondarily connected. The increased retention of lime during the high-fat period in Case 2 (vi) would on this line of reasoning be explained by the increased absorption of vitamin D resulting from the increased intake of fat. The change in the distribution of calcium between phosphorus and soaps and the divergence of the phosphorus from fæces to urine during the high fat period bear a close resemblance to the observations in healing rickets.

In the other two periods, Case 1 (v) and (viii) with high fat the changes in distribution of lime and phosphoric acid, as indicated by the ratios fæcal CaO to fæcal P_2O_5 and urinary P_2O_5 to fæcal P_2O_5 are very similar to those seen in Case 2. The retention of these minerals was, however, greatly reduced, and this despite the fact that a much larger actual amount of fat was absorbed by the patient in these two periods than in the case of Case 2 (vi). Linder and Harris[10] put forward the suggestion that most of the sterols remain with the unabsorbed fat in the gut. Even if this is correct, it would not explain

the marked difference in the results since it would be expected that the greater amount of fat absorbed would carry with it a larger moiety of the sterols. It seems to us that the explanation lies in the larger amount of fat absorbed by Case 1 leading to the production of a ketosis the effects of which overshadow the influence of increased vitamin D absorption. We have shown[11] that the osseous tissues play an important part in getting rid of excess of acid substances, and as a consequence during the administration of an acid-producing substance such as ammonium chloride there occurs a great increase in the excretion of calcium both by the urine and fæces. A similar occurrence takes place in conditions of ketosis. Of the presence of ketosis during the high-fat periods of W.B., further proof is given by the rise in excretion of the titratable acid and ammonia in the urine. In addition, the renal excretion of lime is slightly increased during these periods although the retention is diminished. Admittedly the increase in urinary output is very slight but it must be remembered that the store of lime is much below normal as is indicated by the radiographic evidence of marked osteoporosis. In the high-fat period in Case 2, on the other hand, where a great retention of lime took place the urinary output of this substance was slightly diminished.

If this line of reasoning be correct then it would appear that the low retention of minerals during the high-fat periods of Case 1 must be attributed to the effect of ketosis more than neutralizing the influence of the extra vitamin D made available by the increased absorption of fat. This naturally involves the assumption of a re-excretion of lime by the gut. This view however, is supported by the strong experimental evidence of Percival and Stewart[28] and other workers. Indeed in two of the series recorded here there was much more calcium excreted in the fæces than was ingested :—0·51 grm. in Case 2 (v) and 0·60 grm. in Case 1 (iv).

Effect of NaH_2PO_4.—The effect of NaH_2PO_4 was to decrease the amounts of fæcal calcium and phosphorus although there was a greatly increased ingestion of the latter substance. This must be due either to an increased absorption or diminished re-excretion into the gut. Simultaneously there was a decrease in the amount of fæcal fat although the relative amount of soaps was increased from 47·7 to 57·4 per cent. of the total fæcal fat. The ketogenic action of the increased fat absorption must have been present : therefore it seems safe to assume that the mineral excretion must have played as great a part as in the previous period in combating the acidosis. It would therefore appear that the action of the NaH_2PO_4 was to increase the absorption of lime and phosphorus, so that the increased output resulting from ketosis was rather more than neutralized by the increased absorption. It is impossible to decide whether calcium or phosphorus was primarily affected. It seems reasonable, however, to suggest that the excess of phosphorus in the gut attracted some of the calcium from the fat, and that the combination of phosphorus and calcium was rendered more easily absorbed by the presence of an acid reaction in the gut due to the presence of excess fatty acids and acid sodium phosphate.

Effect of sodium glycocholate.—In one case there was a marked increase in the retention of lime and phosphorus while in the other there was a definite decrease. On the whole this was in conformity with the effect on the absorption of fat since in the second there was an increase in the amount of fæcal fat. With the data at our disposal it is not possible to explain this variability in the action of sodium glycocholate.

Conclusions.—On summing up the findings on mineral metabolism the following conclusions seem justified :—

1. The retention of lime and phosphorus is low while the patient is on a normal diet. The loss of these elements is mainly by the gut. While the retention of calcium is, generally, inversely proportional to the amount of fæcal fat, this is not invariable as an increased retention may occur in spite of a rise in the amount of fat in the motions. The retention of calcium can therefore only be secondarily related to the utilization of fat.

2. Administration of vitamin D raises the retention of lime although the absorption of fat is certainly not increased.

3. Increase in the absorption of fat leads to an increased absorption of lime. If the increased absorption produces a ketogenic effect, the rise in the amount of lime absorbed is masked by an increased re-excretion. The increased absorption of lime is probably the result of an increase in the absorption of vitamin D and an increase in the acidity of the intestinal contents.

4. The effect of rendering the intestinal contents more acid is exemplified by the increased absorption of lime during administration of an acid salt (NaH_2PO_4).

From these findings it would appear that the poor calcium absorption in cœliac disease is due to a lack of vitamin D and inadequate acidity of the intestinal juices. Any factor which leads to an increased utilization of fat containing vitamin D without undue ketogenic effect will produce a rise in vitamin D absorption and consequently an increase in calcium retention as in the sodium glycocholate period of Case 1.

Utilization of carbohydrate (see Tables 3 and 4).—It is a well recognized clinical fact that patients with cœliac disease do not tolerate carbohydrate well. Starchy foods undergo fermentation, and as indicated by the frequent presence of starch granules in the fæces are not well digested. This might, of course, be due to the large bulk of the intestinal contents, which prevents the amylases reaching the starch as quickly as usual, and so allowing fermentation to take place.

The ability of the intestine to absorb simple monosaccharides is very difficult to test. Schaap[12] found values of fæcal carbohydrate higher in cœliac disease than in any other condition. McCrudden [13] on the other hand states that the lower fatty acids which are formed from carbohydrates are if anything less in cœliac stools than normal. Poynton and Cole[14] have reported one case of cœliac disease showing glycosuria : this might have been due to low renal threshold independent of the cœliac condition or possibly was the result of previous carbohydrate starvation. The frequent existence of acetonuria is undoubtedly the result of defective supply of carbohydrate in the diet.

TABLE 3.

BLOOD-SUGAR CURVE IN CŒLIAC DISEASE

Case No.	Wt. in kgrm.	Blood-sugar (mgrm. per 100 c.cm.) after glucose (1 grm. per kgrm. body wt.)					Remarks
		Fasting	30 min.	60 min.	90 min.	120 min.	
1	8·60	77	83	87	79	81	Typical cœliac motions.
	8·60	79	67	73	75	67	,, ,, ,,
	8·60	100	85	79	85	85	,, ,, ,,
2	9·40	77	73	83	77	84	,, ,, ,,
	9·40	95	79	77	73	67	,, ,, ,,
	10·17	58	66	85	66	60	,, ,, ,,
	10·63	67	67	67	67	—	,, ,, ,,
	10·30	104	100	104	100	—	,, ,, ,,
	11·25	63	104	100	122	113	After 14 days' of sod. glycocholate
5	6·54	81	72	72	81	—	Absorp. of fat = 71·3%
6	10·33	106	104	102	98	112	,, ,, ,, = 74·4%
	11·62	82	89	136	109	97	,, ,, ,, = 91·0%
4	5·54	85	106	104	102	100	,, ,, ,, = 91·0%
	5·80	83	87	106	102	100	,, ,, ,, = 68·1%
7	15·5	89	109	109	109	100	Large fatty motions.
	17·0	115	139	170	147	98	Motions apparently quite normal.

TABLE 4.

BLOOD-SUGAR CURVE IN NON-CŒLIAC STEATORRHŒA.

Name	Age	Wt. in kgrm.	Blood-sugar (mgrm. per 100 c.cm.) after glucose (1 grm. per kgrm. body wt.)					Condition of patient
			Fasting	30 min.	60 min.	90 min.	120 min.	
J.T.	10 yr.	17·90	82	134	206	159	109	Chronic intestinal indigestion.
I.W.	1½ ,,	9·80	94	94	122	152	139	Chronic intestinal indigestion.
A.O'B.	7 ,,	22·45	104	143	152	122	—	Tub. peritonitis: absorpt. of fat = 72%
H.D.	3 ,,	14·10	113	146	120	113	100	Chronic intestinal indigestion.
G.L.	6 wk.	5·00	84	106	137	104	102	Biliary atresia.
M.B.	5 ,,	3·10	95	177	134	120	118	Biliary atresia.
M.M.	9 yr.	24·85	72	152	199	50	50	Catarrhal jaundice.

The fasting blood sugar is reported as being very variable but frequently low. The behaviour of the blood sugar after administration of glucose has been investigated by several authors. Fanconi[3] reports varied results. Generally the rise of blood sugar after ingestion of glucose was very slight or even nil, but occasionally a normal or prolonged rise was noted. McLean and Sullivan[15] obtained flat blood-sugar curves after 1·75 grm. glucose per kgrm. body weight, and in some patients even after as much as 9 grm. per kgrm. Administration of lævulose or galactose led also to no rise of blood sugar, although in two cases galactosuria was found. Thaysen[16], and Thaysen and Norgaard[17] report a subnormal rise of blood sugar after the ingestion of 1 grm. of glucose per kgrm. bodyweight.

In our series the fasting blood sugar was normal or subnormal, thus falling into line with the observations of other investigators. During the active stage of the disease, as indicated either by clinical manifestations or metabolic results, the administration of either glucose or lævulose led to an insignificant rise of blood-sugar. During a period of convalescence, resulting from dietetic treatment or otherwise, the blood-sugar curve becomes more normal in type. The low blood-sugar curve seems to be pathognomonic of the active stage of true cœliac disease. In Table 4 are noted the values of the blood sugar curves found in six cases of non-cœliac steatorrhœa: in all the curve is normal in height. The abnormality in the curve therefore cannot be due to the excessive bulk of the intestinal contents.

The flat blood-sugar curve in cœliac disease might be due either to an increased glycogenic function of the liver or to a greatly delayed intestinal absorption. It is unlikely that there is any increased glycogenic function since the low blood-sugar curve still persisted even when the patient was on a high fat diet. It is well recognized that such a diet raises the height and prolongs the fall of the blood-sugar curve. Accordingly the increase in glycogenic function should have been impaired; instead of this the blood-sugar curve was just as flat as when the subject was on a normal fat-intake. The rise of the blood sugar after subcutaneous injection of adrenalin was quite within normal limits, thus affording further evidence that as far as carbohydrate metabolism is concerned hepatic function is normal.

Thaysen[16] has argued against defective absorption being the cause of the low blood-sugar curve on the following grounds. (1) The blood sugar is also lower than normal after intra-venous injection of glucose. (2) The R.Q. rises to about unity after ingestion of glucose. (3) The R.Q. is higher on a carbohydrate diet than on an ordinary mixed diet. He believes that the cause is some toxic effect on the endocrine glands. None of the objections advanced carry much conviction. No mention is made of change in blood volume after intra-venous injection of glucose and without information on this point it is impossible to determine whether the difference in blood sugar is due to disturbance in carbohydrate metabolism or to alterations in the concentration of the blood. It is possible that the diminished blood sugar is a result of the passage of a greater volume of fluid than normal from the blood stream. The evidence from the R.Q. results is also equivocal. First, it has been shown by Cathcart and Markowitz[18] that the value of the R.Q. being really the resultant of all

the metabolic processes does not necessarily indicate the metabolism of any particular food material. Secondly, it is not denied that absorption of carbohydrate does take place. It is merely a delay in absorption that is postulated. Accordingly the fact that the R.Q. is raised during a high carbohydrate intake is evidence solely that more glucose is oxidized and not that it is absorbed as quickly as normal.

Thaysen and Norgaard[17] hold the view that the abnormality in carbohydrate metabolism is due to some toxic effect on the endocrine glands. The evidence in support of this is a slightly hypernormal rise of blood sugar after the subcutaneous injection of epinephrine. In the few instances in which we have investigated the action of epinephrine we have found that the rise in blood sugar is quite normal when compared with the results obtained in normal children.

It has already been pointed out that the abnormality in glucose metabolism is not due to the bulk of the fæces mechanically impeding absorption. In this connection it is interesting to note the normal blood-sugar curve in a child suffering from tuberculous peritonitis in whom the percentage absorption of fat was much below normal. The defective utilization of fat was due to the blockage of the lacteals, leaving the intestinal epithelium unimpaired and thus allowing normal absorption of all blood-borne foodstuffs. In cœliac disease on the other hand it would seem that the intestinal epithelium or its immediate environment is at fault, so accounting for defective absorption of both fat and glucose.

Utilization of protein (see Table 5).—Herter[19] concluded that although absorption of protein in cœliac disease is better than that of fat it is still not

TABLE 5.

SHOWING OUTPUT OF NITROGEN IN THE FÆCES.

Case No.	Intake of N. per day grm.	Nitrogen in fæces		
		Output per day grm.	As % of dried fæces	As % of intake
1 (iii)	3·521	0·305	2·0	8·7
(iv)	3·111	0·414	1·3	12·9
(v)	2·991	0·302	2·6	10·1
(vi)	3·939	0·154	2·6	3·9
(vii)	4·239	0·271	1·8	6·4
(viii)	4·135	0·230	2·0	5·6
2 (v)	5·998	0·235	1·2	3·9
(vi)	5·058	0·209	1·2	4·1
(vii)	5·617	0·271	1·5	4·8
3 (i)	3·760	0·711	4·5	19·0
(ii)	3·431	0·464	1·9	13·5
(iii)	3·617	0·550	1·7	15·2
(iv)	3·601	0·520	1·9	14·4
5 (i)	5·14	1·05	3·7	20·4
(ii)	3·81	2·04	5·5	53·5

as good as in health. Schaap[12] found that the percentage of nitrogen in the fæces was practically the same as normal: owing to the excess in the amount of fæces passed there was naturally a much greater loss of nitrogen than in health. McCrudden and Fales[20] maintain that the nitrogen in cœliac fæces is derived from the same source as in health, i.e., chiefly from the intestinal secretion. In one case a five-fold increase of nitrogen intake was actually accompanied by a reduction in the nitrogen content of the fæces. They conclude that the high fæcal output of nitrogen in cœliac disease is due not to defective absorption but to re-excretion. Fanconi[3], on the other hand, states that with rich protein intake relatively more nitrogen appears in the fæces both in normals and cœliacs. He gives figures which show that in mild cœliac disease about 16 to 20 per cent. of the nitrogen intake appears in the fæces, while in severe cases as much as 48·7 to 63·6 per cent. This is shown even more

TABLE 6.

CHEMICAL ANALYSIS OF BLOOD.

Case No.	Serum		Plasma	Blood		
	Calcium mgrm. %	Phos. mgrm. %	Fatty ac. as grm. tripalmitin per 100 c.cm.	Chlorine mgrm. %	CO_2 vol. %	NPN mgrm. %
Normal			330–500	280–340	40–60	20–40
1	7·8	4·7	376	310	47·2	35·1
	—	—	405	—	—	—
2	7·7	3·0	354	340	57·6	—
	7·1	2·7	410	290	—	29·6
3	—	—	387	325	51·2	37·4
4	7·0	3·0	—	—	—	—
	6·3	2·0	—	—	—	—

clearly when the fæcal nitrogen is computed as a percentage of the total excreted: in the normal this is 13 to 20 per cent. in the mild cœliac 19 to 27 per cent.: in the severe 43·7 to 52·1 per cent.

Our results show a much smaller percentage of nitrogen in the fæces than do those of Fanconi, probably because of the easily absorbable nature of the proteins (milk) given to our patients. The nitrogen percentage of the dried fæces seems to be quite within normal limits so that any excess in nitrogen loss must be the result of the great fæcal weight. In three instances in our series a high percentage of nitrogen was found in the dried fæces: in these periods 19·4, 20·4, and 53·5 per cent. of the total intake of nitrogen was found in the motions. These results occurred simultaneously with a defective absorption of fat. It would appear, therefore, that in an acute stage of the disease the absorption of protein is hindered both relatively and absolutely, but not to the same extent as fat.

In two instances the ability of the patient to absorb urea from the intestine was tested : in both the excretion was normal both as regards time and amount. It seems, therefore, that whatever fault is in the intestinal utilization of nitrogen, it is not concerned with simple nitrogenous substances but with complex molecules.

Discussion.

The most striking feature in the chemical pathology of cœliac disease is undoubtedly the abnormality in the utilization of fat. All attempts to formulate a conception of the pathogenesis of the condition have been based on this abnormality. Generally speaking it has been held that the defect is one of absorption, but Moncrieff and Payne[21] have tentatively suggested that the abnormality is one of defective intermediate metabolism, possibly a result of the impaired action of blood or tissue lipase. In a preliminary communication they have given figures for blood fat in cœliac disease which are in excess of those obtained from normal individuals. It is exceedingly difficult to obtain blood in different individuals when the intermediate metabolism of fat is at the same stage, as the various conditions affecting the migration of fat to and from the tissues are in great part unknown. We have estimated the blood fat in a few cases (Table 6), and have found all the values within the normal range which admittedly in a wide one. Fanconi[3] reports low, normal, or even subnormal values for the blood fat in the fasting condition. He further states that in cœliac disease the blood fat curve after oral administration of olive oil or butter is flatter than normal. These results indicate that whatever the state of intermediate fat metabolism the defective utilization is not the result of a high blood fat hindering absorption or promoting re-excretion into the gut.

Further evidence has been brought forward to show that carbohydrate is absorbed with more difficulty than normal. Another substance showing a defective absorption-curve is acid sodium phosphate (Fig. 2). On the other hand, oral administration of sodium chloride or urea led to the output of these substances quantitatively in the urine as speedily as in the normal individual. Methylene blue appeared in the urine as soon after ingestion as it did in the normal subject. It is possible that the apparently normal absorption of urea, chloride, and methylene blue may be due to the fact that these substances pass through the intestinal epithelium by the simple physical process of diffusion. Fat, glucose and protein probably require a more complex set of conditions such as narrow limits of pH, presence of bile-salts and so forth. It must be emphasized again that the defect in carbohydrate absorption cannot be attributed, unless in a minor degree, to the mechanical interference of the large amount of fat, since in the case of steatorrhœa due to tuberculous peritonitis the absorption of carbohydrate and protein was quite normal.

There is no evidence of any structural change in the intestine which could account for the grave defect in absorption. Lehndorff and Mautner[22] sum up the post-mortem findings by saying that in general, the atrophy of the organs produced in cœliac disease is a result of the hunger condition. In two of our patients who died the pathological reports (for which we are indebted

to Dr. J. W. S. Blacklock), indicate that no abnormalities either macro- or micro-scopic were noted in the gastro-intestinal tract, while in only one was there atrophy of liver and spleen.

Freise and Jahr[23] attributed the defective fat absorption to an over-rapid passage of the chyme through the intestine. They have been able to increase the percentage utilization of fat by slowing the movement of food through administration of opium or atropine. Meyer[24] points out that fat-splitting also suffers as a result of increased rapidity of the passage of food through the bowel. In cœliac disease, however, fat-splitting is usually quite normal. In two cases we have followed the passage of a barium meal radiographically, but no abnormality was noted in the times taken to complete the various stages.

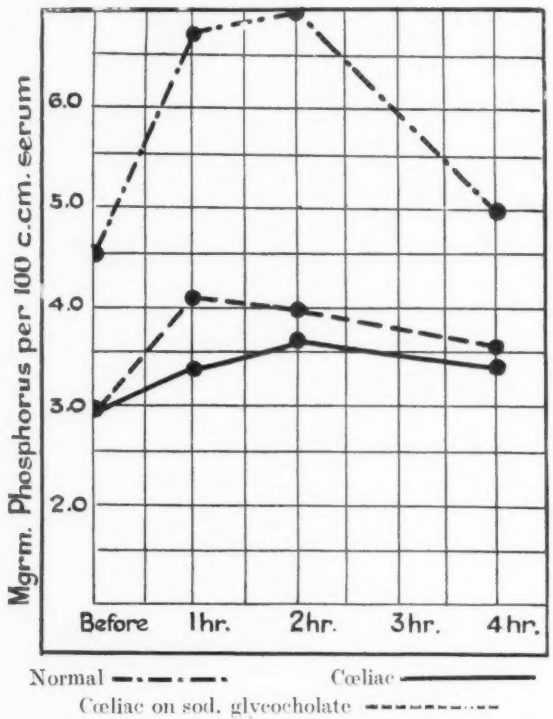

FIG. 2. Inorganic phosphorus content of serum after oral administration of NaH_2PO_4

Further, carmine or charcoal ingested orally did not appear any more rapidly in the fæces of the cœliac patient than in the normal. The improvement resulting from the administration of opium was probably due to slowing down of the passage of the chyme, thus allowing longer contact between food material and intestinal epithelium. The defect in cœliac disease is after all not an absolute one. The state of affairs might be compared to a catalytic reaction taking place in the presence of an insufficiency of catalyst.

It has been clearly shown that the abnormality is not present in the intermediate metabolism, nor can it be detected either in the intestinal epithelium or in the rate at which the intestinal contents pass. It would seem therefore that the fault lies in some physico-chemical abnormality of the intestinal contents.

The absence or paucity of bile in the intestine has long been suggested as the cause of the mal-absorption of fats in the cœliac state. The whitish colour of cœliac motions has been attributed to absence of bile products. These, however, can be demonstrated both in the fæces and the duodenum. It is generally held that the normal fæcal colour is masked by the excess amount of fat. Nevertheless it is quite possible that although the bile pigments are present, there may be a defective supply of bile-salts which, after all, for purposes of absorption form the all-important constituent of the bile. Miller, Webster, and Perkins[25] in 1920 published results of three cases treated by bile-salts. Unfortunately in only one case was a complete metabolic determination performed, and in it improvement was not marked as the child during the control period had commenced to improve spontaneously. The percentage absorption of fat was only increased from 85·8 to 87·0. In the other two

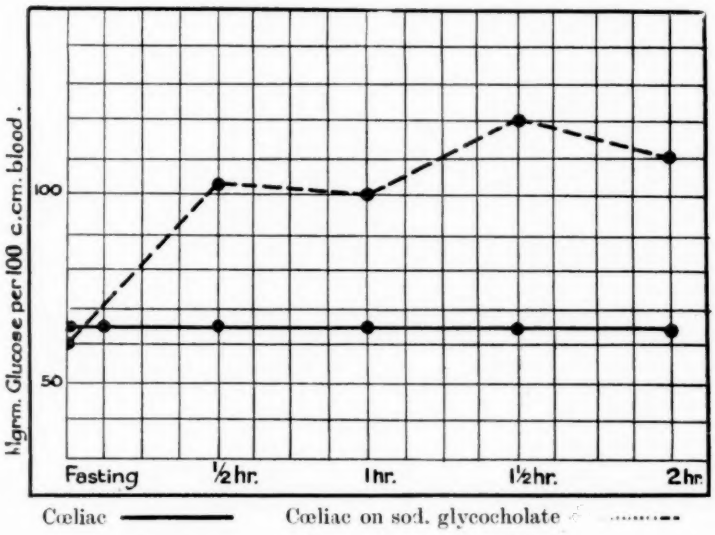

FIG. 3. Blood sugar curve in cœliac disease.

cases only the fæcal content of fat was estimated and this was certainly reduced with bile-salt treatment. The work, therefore, while strongly suggestive of the beneficial action of bile-salts on the absorption of fat is not conclusive. Fanconi[3] could get no definite improvement by the use of bile-salt preparation (decholin). Bischoff[26], however, found that this substance led to an increased retention of fat and calcium : he could arrive at no conclusion as to the ætiological relationship between cœliac disease and bile-salt absence. Our own results are conflicting. In one there was definite improvement in fat and mineral absorption, but in the other there was quite a marked decrease in the retention of these substances. In one case (Fig. 3) the blood-sugar curve gave evidence of more normal carbohydrate absorption during the administration of bile-salts. Against the view that the absence of bile-salts is the important factor in the chemical pathogenesis of cœliac disease is the

great difference of the metabolic picture in states such as atresia of the bile duct where there is complete absence of bile. In such a condition the bulk of the phosphorus appears in the urine while the blood-sugar curve is quite normal in type. Administration of bile-salt in biliary atresia does not lead to increased retention of minerals (Table 7).

One other point brought out in the course of this series of observations seems to be the beneficial effect of acid sodium phosphate both on fat and mineral metabolism. It is difficult to believe that this benefit is the result of phosphorus as such, and it would seem probable that its action is due to its acid nature. It is now largely accepted that increasing the acid reaction of the intestinal contents leads to a better absorption of lime and phosphorus. Further, the production of bile is stimulated by secretin which is also the result of the action of acid on the intestinal epithelium. The administration of an

TABLE 7.

SHOWING EFFECT OF BILE-SALT ADMINISTRATION ON MINERAL METABOLISM IN A CASE OF BILIARY ATRESIA: DAILY INTAKE, OUTPUT AND RETENTION.

Diet	Days	CaO (grm.)					P_2O_5 (grm.)				Urine P_2O_5 / Fæcal P_2O_5 × 100	Fæcal CaO / Fæcal P_2O_5 × 100	Retention grm. per kgrm. body weight	
		Intake	Fæcal output	Fæcal output as soaps	Urinary output	Total retention	Intake	Fæcal output	Urinary output	Total retention			CaO	P_2O_5
Cow's Milk 540 c.cm. + sugar grm. 24	5	0·837	0·8105	0·4290	0·0186	·0079	1·161	0·4711	0·560	0·130	118·8	172·0	·002	·03
Cow's milk 540 c.cm. + sugar grm. 24 +sod. glycocholate	6	0·837	0·8061	0·6507	0·0128	·0181	1·161	0·5303	0·5973	0·0337	112·6	152·0	·004	·008

acid salt should therefore favour both the absorption of minerals and the production of bile-salts. Verzàr and Kúthy[8] have shown that the presence of bile-salts permit the absorption of soaps at an acid pH. In the absence of these salts the absorption of fats as soaps is impossible unless at a pH of 9·0. If accordingly the reaction of the cœliac intestine were alkaline, but not, of course, with as high a pH as 9·6, there would be a defective absorption of minerals and a defective flow of bile. Shift of the reaction to the acid side would thus facilitate the absorption of lime and phosphorus and simultaneously increase the amount of bile in the intestine thus raising the utilization of fat. If with the added amount of fat there is also absorbed more vitamin D, the fixation of the calcium and phosphorus in the bone would naturally follow.

Summary.

Summing up, it appears that the results obtained in metabolic investigations on cœliac disease may be at present best explained on the following assumptions :—

(a) The defect is one of absorption and is due to change or changes in the physico-chemical constitution of the intestinal contents.

(b) These changes probably include a shift of reaction to the alkaline side and a deficiency in the bile-salts.

(c) The poor retention of minerals is probably the result of the alkaline reaction of the contents of the gut together with a difficulty in vitamin D. Improvement in the retention of minerals may occur without synchronous improvement in fat absorption.

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APPENDIX.

Case 1.—W. B., male, was admitted to hospital on May 25th, 1927, at the age of 2 years and 10 months, with a history of diarrhœa and vomiting since he was 11 months old. He was small—wt.=8·68 kgrm.—ht.=77 cm. (normal 87 cm.) with a prominent abdomen. The stools were large, pale and offensive. During residence in hospital diarrhœa continued with short periods of improvement. His weight on dismissal 10 months later (March 28th, 1928) was 7·36 kgrm. Symptoms continued after dismissal and on May 14th, 1928, he was re-admitted. Weight was then 7·8 kgrm. On Sept. 10th, he took diphtheria and later scarlet fever. He was removed to a fever hospital. On March 11th, 1929, one year and ten months after his first admission, he was re-admitted because of persistence of the diarrhœa. His weight was 8·61 kgrm. He was dismissed 5 months later at the age of 5 years with a weight of 7·43 kgrm.

Case 2.—E. A., female, was admitted to hospital when 4 years old with the following history: Healthy at birth but at 3½ months weighed only 6¼ lb. and motions were bulky and pale. This continued with occasional intervals of improvement of from 2 to 3 weeks. She was small and spare—wt.=8·48 kgrm.—ht.=78 cm. (normal 96·7 cm.) with prominent abdomen. She was kept in hospital for 3½ months and stools continued pale and offensive with periods of improvement of from 1 to 3 weeks. On dismissal weight was 10·0 kgrm. Five months later she was re-admitted because of return of diarrhœa and loss in weight. Weight on re-admission was 9·4 kgrm. The attacks of diarrhœa became gradually less frequent, and on discharge one year later, when she was 5½ years old, the weight had increased to 14·18 kgrm.

Case 3.—M. R., female, aged 4 years and 10 months, was admitted with a history of prominence of the abdomen and attacks of diarrhœa for 2 years. She was small—wt.=8·8 kgrm.—ht.=78 cm. (normal 105·3 cm.) with a prominent abdomen. The stools were pale and bulky. She was kept in hospital for 6 months during which time diarrhœa continued with occasional periods of improvement. The weight on dismissal was 9·0 kgrm.

Case 4.—J. S., male, was admitted on August 21st, 1929, when 2 years and 2 months of age. Except for a convulsion when 11 months old he throve well until 1 year and 10 months, when attacks of vomiting and diarrhœa appeared and the weight began to fall. He was emaciated and dehydrated—wt. = 5·95 kgrm.—ht. = 75 cm. (normal 82·8 cm.). The stools were frequent, and green with numerous curds and much mucus. During residence in hospital there was but little gain in weight and the stools were frequently large, pale and offensive. Weight on dismissal 3 months later with measles was 6·65 kgrm. On Feb. 12th, 1930, he was re-admitted. He had made a good recovery from measles and had remained well until 2 weeks before re-admission when diarrhœa and vomiting returned, the stools being bulky and pale. He was emaciated—wt. = 6·8 kgrm.—and Chvostek's sign was positive. Two weeks later carpo-pedal spasm appeared and was relieved with large doses of calcium chloride (30 grm. six times daily). Chvostek's sign reappeared on March 18th, and from April 2nd 2 pellets of radiostol were given twice daily.

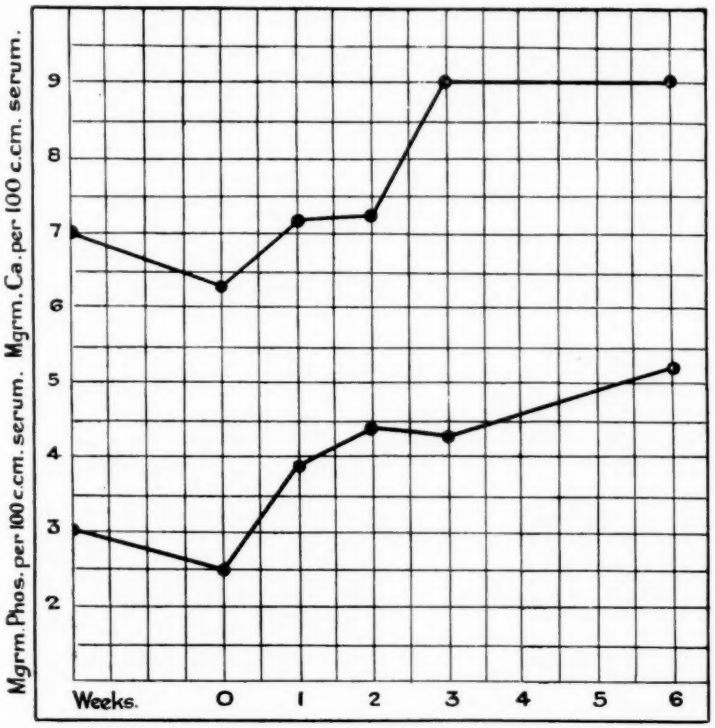

FIG. 4. Case 4. Change in calcium and inorganic phosphorus content of serum during treatment with radiostol.

The behaviour of the calcium and inorganic phosphorus content of the blood serum during this period of treatment is shown in Fig. 4. It is of interest to note that both the calcium content and inorganic phosphorus content of the serum were low, a finding not uncommon in cases of rickets complicated by tetany, and that during treatment with radiostol there occurred a gradual increase in both. All clinical evidences of tetany disappeared in 2 weeks. Radiological examination of the bones showed no evidence of rickets.

The child continued to have large pasty motions, and on June 26th he took diphtheria and was dismissed, weighing 6·36 kgrm. He was re-admitted on August 6th and died suddenly within 24 hours. The post-mortem examination revealed atrophy of the spleen, liver and kidneys. here was no abnormality detected in any part of the stomach or intestines.

Case 5.—M. McC., female, was admitted on January 8th, 1930, aged 1¼ years. She had thriven well until 1 year old, when motions became pale and bulky, and she ceased to gain in weight. Weight on admission was 6·8 kgrm. and height 73 cm. (normal 74 cm.). Stools continued to be frequent, pale and bulky, and her weight fell steadily. On February 12th, 5 weeks after admission, when the weight had fallen to 5·3 kgrm. she died. Post-mortem examination revealed a few patches of broncho-pneumonic consolidation throughout the lungs. There was no atrophy of any of the organs. Irregular areas of congestion of the mucous membrane occurred throughout both large and small bowel.

Case 6.—A. F., male, aged 3 years. For 6 months previous to admission he had been losing weight, had vomited and had frequent loose motions. He was small and pale—wt.=11·14 kgrm. —ht.=78 cm. (normal 89·1 cm.). Stools were frequent, large and pale. He was kept in hospital for 5 months and attacks of diarrhœa continued with occasional intervals of improvement lasting 2 to 4 weeks. Weight on dismissal was 11·17 kgrm.

Case 7.—M. L., a private patient under the care of Dr. L. Findlay. The child was aged 3½ and 4 years at the time of the two blood-sugar tests (Table 3).

A METHOD OF STUDY OF INTRACRANIAL HÆMORRHAGE IN THE NEW-BORN INFANT

BY

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Within recent years increasing attention has been paid to intracranial hæmorrhage in the newly-born, not only in those infants who survive, but also in the demonstration of the hæmorrhage at necropsy. The difficulty in removing the cranial vault in an infant and the extreme softness of the brain substance render any attempts to determine the position and amount of the injury by ordinary post-mortem methods almost impossible. Acting, therefore, upon the suggestions of Schoenholz[3] and of Roberts[2] the procedure described here was adopted to obviate these difficulties and thus to determine by radiograms the presence, site and size of intracranial hæmorrhage.

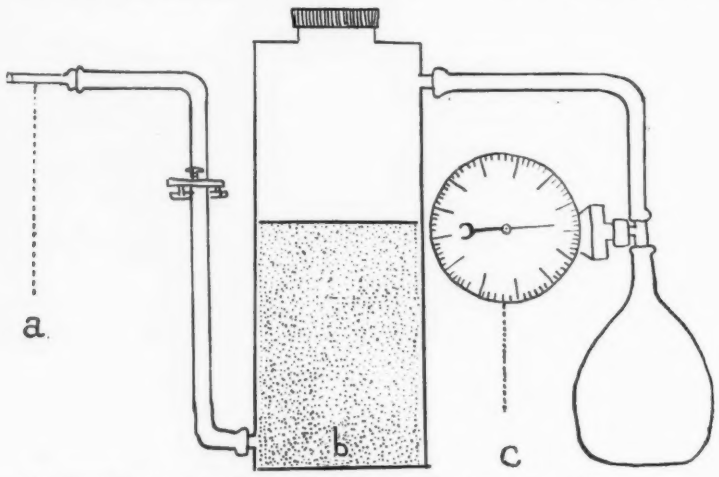
Schoenholz, by injecting solutions of red lead into the cerebral vessels, was able to show by means of X-rays the gross changes within the cranium as a result of extravasation from the damaged vessels. Roberts used metallic mercury and, in some cases, iodized oil. Benefiting by the experience of Campbell[1] we used Röntyum (Kahlbaum) and obtained stereoscopic radiograms to assist in the study of the condition. By the use of Röntyum the difficulties of the previous workers have been reduced, as excellent definition is obtained and the finest possible detail of the circulation is obtained since the emulsion does not gravitate.

The apparatus is easily devised as will be seen from Fig. 1. It consists of a metal container (b) with an inlet tube at the upper end and an outlet at the lower. A screw stopper is advisable. The emulsion is prepared by mixing 40 grm. of Röntyum with about 75 c.cm. of distilled water in a mortar. Thorough emulsification is essential and about twenty minutes is required in its preparation to obtain a satisfactory suspension. The container is filled with the Röntyum emulsion and the inlet tube is connected with the bulb, an aneroid manometer (c) intervening so that the pressure within the system may be controlled. The outlet tube is connected with a serum needle (a), the bevelled point of which has been removed. A clip on the outlet tube is useful as an additional control. All connections should be carefully reinforced with fine wire.

The carotid artery is the usual site of injection and it is easily found just above the inner end of the clavicle. A ligature is passed under the vessel and a small longitudinal incision is made in the wall. All air is driven out of the system by gentle pressure of the bulb until the Röntyum appears at the needle which is then inserted into the vessel and tied in position. The umbilical vessels may be used, thus obviating the necessity for dissection, but injection

by this route must be made within a few hours of birth, and on account of the changes which occur in the cord after birth is quite unsuitable in those cases in which the infant has survived for more than twelve hours. In still-born infants, however, this route is quite satisfactory and more convenient. When the needle is fixed in the vessel the pressure is gently but steadily raised until the manometer records about 230 mm. of mercury, and this pressure is maintained for about twenty minutes, by which time from 50 to 60 c.cm. of the emulsion will have been injected. The radial artery may be exposed and incised to indicate when the arterial system has been filled and also to act as a safety valve. We have not noted rupture of vessels when the suggested pressure has been maintained and our experience would indicate that much higher pressures fail to cause damage to the vessels. Higher pressures are, however, unnecessary as the finest arterioles are filled at a pressure of 230 mm. of mercury.

When the arterial system is filled a stereoscopic radiogram is taken and the exact location of the hæmorrhages is determined by study of the stereo



(a) Transfusion needle. (b) Metal cylinder. (c) Manometer.

FIG. 1.

picture. In our experience Röntyum has been very successful as it does not tend to gravitate even after twenty-four hours; it penetrates the finest arterioles and gives excellent definition. Metallic mercury as used by Roberts has the disadvantage that it tends to sink to the lowest level. Röntyum is considerably less expensive than mercury, and recovery on the grounds of economy (as with mercury) is not worth while. Iodized oil eliminates the difficulty of gravitation, but has the disadvantage of lack of definition in the radiogram.

When permission to perform a post-mortem examination is refused the Röntyum may be injected via the umbilical vessels and radiograms obtained without any evidence of interference. When the carotid artery is exposed there is very little mutilation, and parents are spared the heartaches that so often accompany the ordinary post-mortem examination. The information gained by this method as to the site, size and number of the hæmorrhages is even more accurate than that obtained by the most careful post-mortem technique, and the record may be filed for future reference.

It is not our purpose at present to give the results of our study of intracranial hæmorrhage by this method, but we would emphasize that as the Röntyum emulsion circulates exclusively in the arterial system, the extravasation of blood must be from ruptured arterial vessels. We have compared the picture obtained by traumatic post-mortem rupture of a vessel and subsequent injection, and have noted that the shadow of extravasated Röntyum is altogether different from that which occurs when the emulsion passes into a clot of blood. We have also confirmed at necropsy that the limits of the Röntyum are deter-

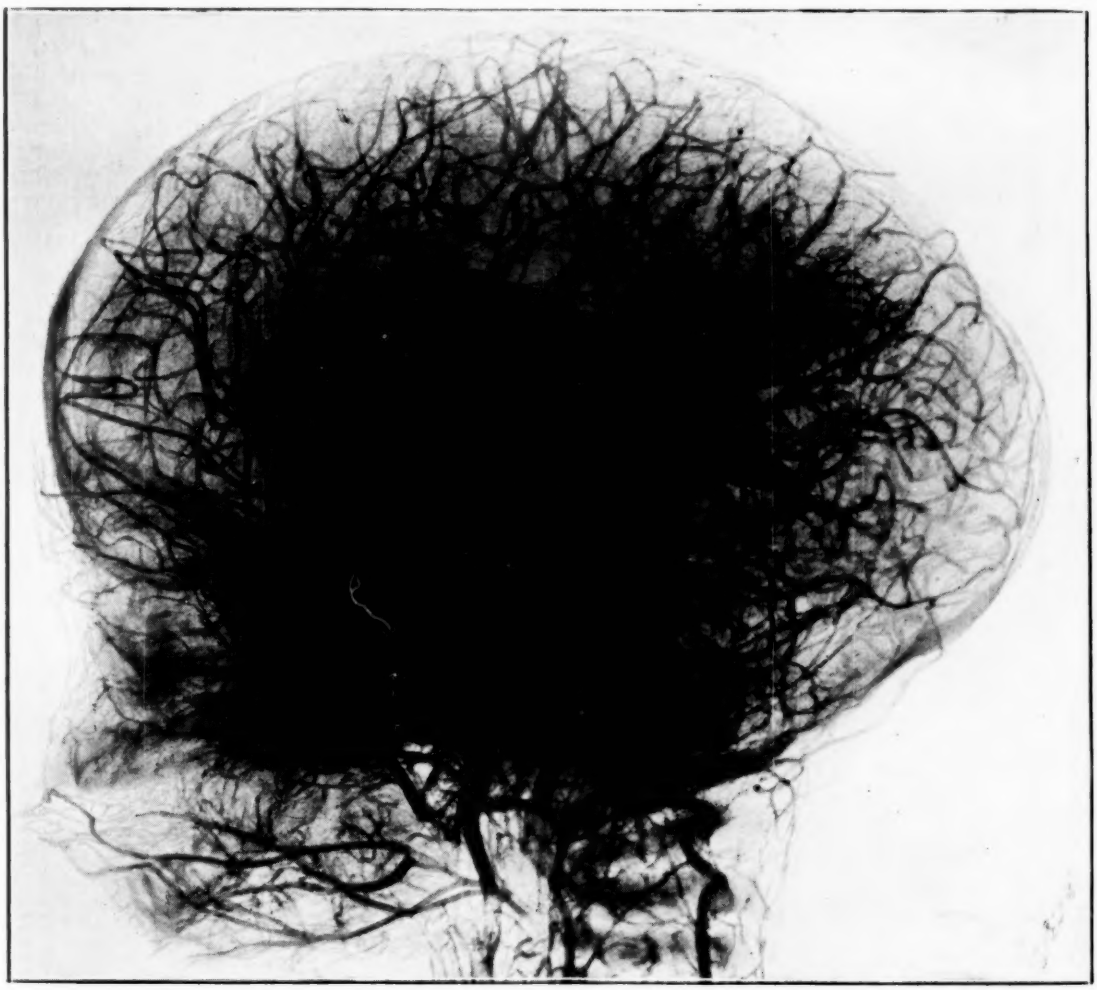


FIG. 2. Intra-ventricular hæmorrhage in still-born infant.

mined by the size of the original blood extravasation. In addition, the control of the pressure by the manometer and the severed radial artery acting as a safety valve are sufficient guarantees against damage to the vessels by the injection.

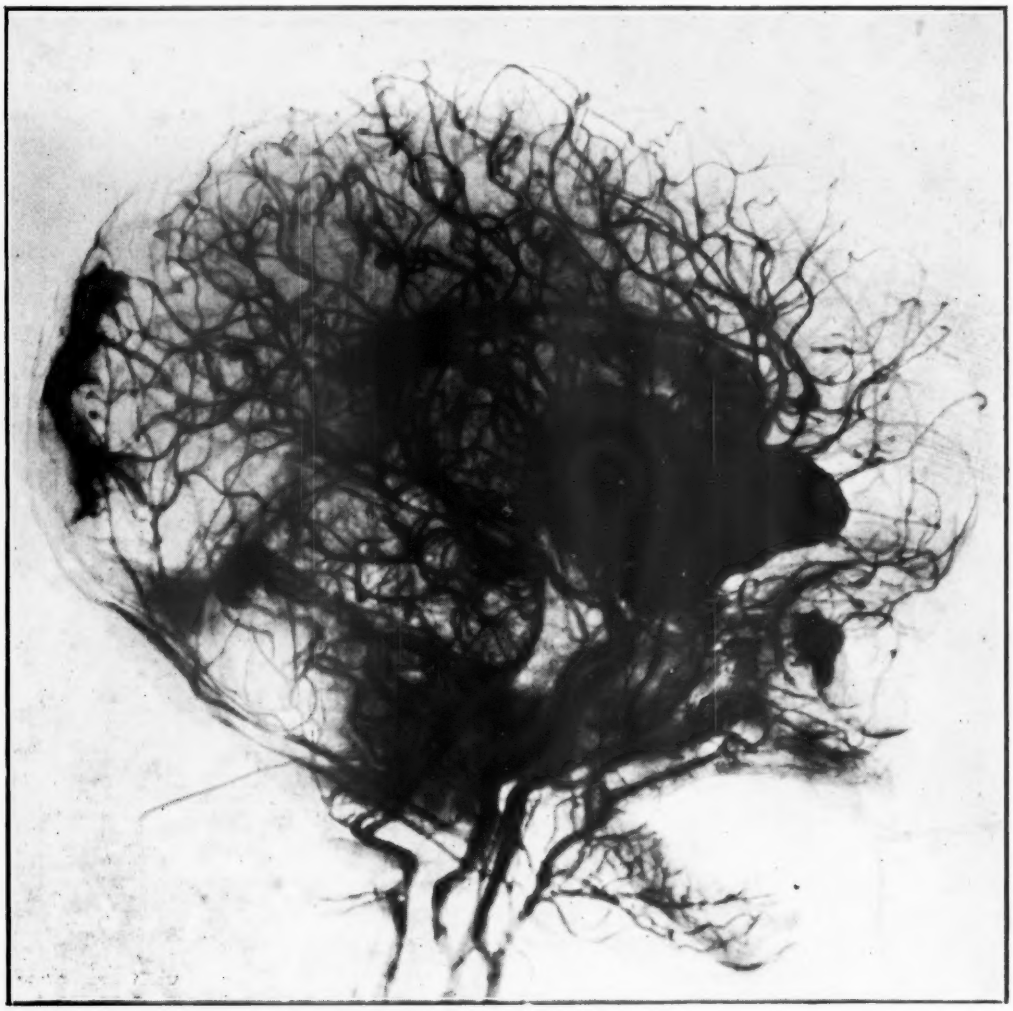
Fig. 2 shows the radiogram in a case of intra-ventricular hæmorrhage in a still-born infant. Fig. 3 is an example of a large hæmorrhage in the right temporal region with smaller ones in the region of the tentorium and in the retina.

Summary.

A method of study of the occurrence, site, size and number of hæmorrhages in cases of intracranial hæmorrhage is described.

The advantages of this method are that permission to perform a necropsy is unnecessary as there is practically no mutilation of the body. The technique is simple, the injected Röntyum is inexpensive, gives excellent definition and does not tend to gravitate. Accurate localization by stereoscopic radiogram is possible and a permanent pictorial record can be kept.

POSTERIOR



ANTERIOR

FIG. 3. Large hæmorrhage in the right temporal region with smaller ones in the region of the tentorium and in the retina.

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2. Roberts, M. H., *Am. J. Dis. Child.*, Chicago, 1929, XXXVIII, 1196.
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TWO CASES OF SUB-ACUTE HEPATIC NECROSIS

BY

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The two following cases of hepatic necrosis in children seem to be worth recording: one for its extreme youth (8 months) and its wholly puzzling ætiology; and the other for its apparent connection with epidemic catarrhal jaundice.

Case reports.

Case 1.—A girl baby, aged 8 months, was brought to the East London Hospital for Children with the complaints that the abdomen had been swelling and that the child was occasionally yellow. She had had broncho-pneumonia, not severely, six weeks previously, and before that had been perfectly well. She was the first child of a young couple, aged 20 and 21 respectively, both healthy. There had been no miscarriages; she was born at full term and weighed 9¼ lb. at birth, was being breast-fed entirely and had gained weight steadily until her illness.

On admission the child was found to be well developed and well nourished, weighing 15 lb. 12 oz. She looked very pale with a sub-icteric tinge, though with no icterus of the scleræ. No teeth. No sign of rickets in epiphyses. Chest normal.

The abdomen was protuberant, with some enlarged veins in the wall, running from groin to thorax. The liver was much enlarged, the edge being below the umbilicus; it was hard and firm, no nodules could be felt and it was evidently not tender. The spleen was also enlarged, firm and smooth; its tip was at the level of the umbilicus. Urine: no albumin, sugar, pus or bile; not tested for urobilin. Blood: red blood corpuscles 2,390,000 per c.cm., hæmoglobin 48 per cent., white blood corpuscles 20,000, fragility of red cells normal. Mantoux reaction negative.

Wassermann reactions were tried on more than one occasion, and Kahn once. They gave the following results:—

Jan. 21st. Baby doubtful positive. Mother negative. Father negative.
Feb. 11th. Baby negative.
Feb. 18th. Baby positive after a small dose of sulpharseno-benzine.
Feb. 18th. Baby Kahn reaction positive.

Course.—During the first four weeks the child was in hospital there was no improvement in the general condition. Such jaundice as had been present disappeared, but the anæmia increased. A week after admission both kidneys could be felt behind the enlarged liver and spleen, a fact which further complicated the diagnosis, as they were evidently much swollen. The glands of the neck and axillæ also became somewhat enlarged. The size of the spleen diminished; the liver remained enlarged and the abdominal veins became more dilated.

Owing to the doubtful Wassermann test in the first instance, a repetition was made after a provocative dose of sulpharseno-benzine, with a positive result; the Kahn test was also positive. On this result it was decided to institute anti-syphilitic treatment; accordingly the child was given mercury and iodide, together with injections of sulpharseno-benzine. In the light of later events it would seem that this course was probably unwise and not only added complexity

to the diagnosis but possibly hastened the end by contributing another poison, namely arsenic, to the over-burdened liver. The absence of any other signs of syphilis in the infant, together with the clean history sheet of the first few months of life, were of more importance on the negative side than a complement-fixation test on the positive side.

The child lived about two months in hospital, that is probably between three and four months altogether from the onset of symptoms. During the week before death the temperature was raised, otherwise the disease had been afebrile.

AUTOPSY.—The liver was enlarged and stained greenish yellow. The surface was finely nodular, the nodules varying in size from a pin's head to a small pea, somewhat flattened and at no point very prominent. The liver substance did not feel hard and cut without resistance. The cut surface showed much bile staining, the lobular arrangement was lost, completely in some parts, partially in others, and there was an appearance of new fibrous tissue irregularly arranged.

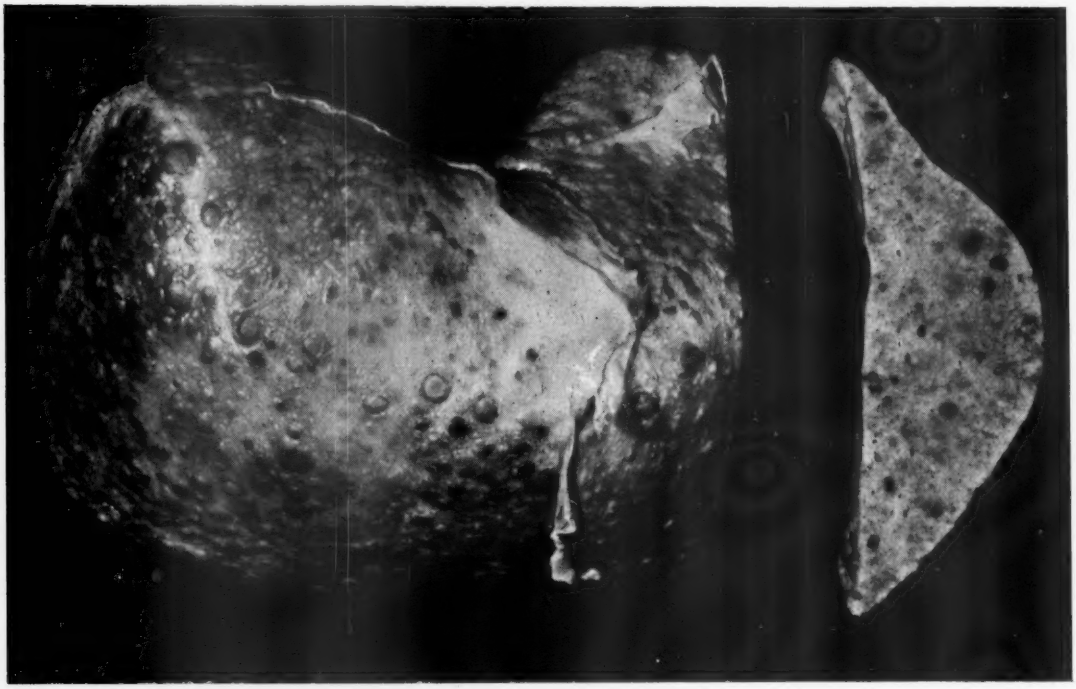

FIG. 1. Case 1. Liver with cross section.

The spleen was enlarged but showed no gross changes. Both kidneys were much enlarged, about one and a half times the normal size, were pale, and showed general swelling of both cortex and medulla.

Microscopically, the destruction of liver cells was irregular in distribution; even in those parts of the organ where necrosis was at a minimum there was considerable fibro-cellular infiltration and an interference with the lobular arrangement. In the areas of maximum destruction very few liver cells remained, and none in orderly arrangement. There were chiefly masses of fibro-cellular tissue, isolated cells and innumerable sprouting bile-ducts defining either old or regenerating lobules. The latter showed vigorous but evidently unsuccessful attempts at hyperplasia, as most of the new cells were loaded with fat. Levaditi staining showed no evidence of syphilis in the liver. The kidneys showed much swelling and degenerative changes of the parenchyma. The lymphatic glands of neck and axillæ, which had been enlarged for a period during life, had returned to normal size. There were no changes in the lungs, heart or brain.

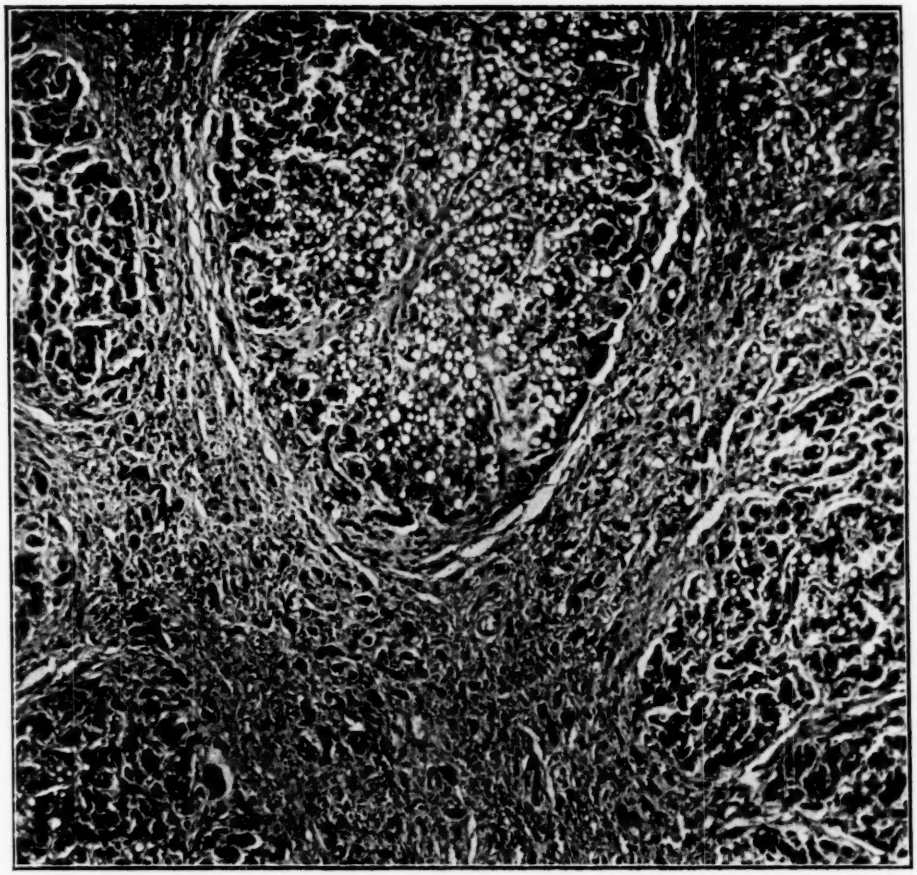

FIG. 2. Case 1. (Low power). Regeneration nodule on surface of liver, showing much fatty change and embedded in fibro cellular matrix rich in sprouting bile-ducts and isolated parenchyma.

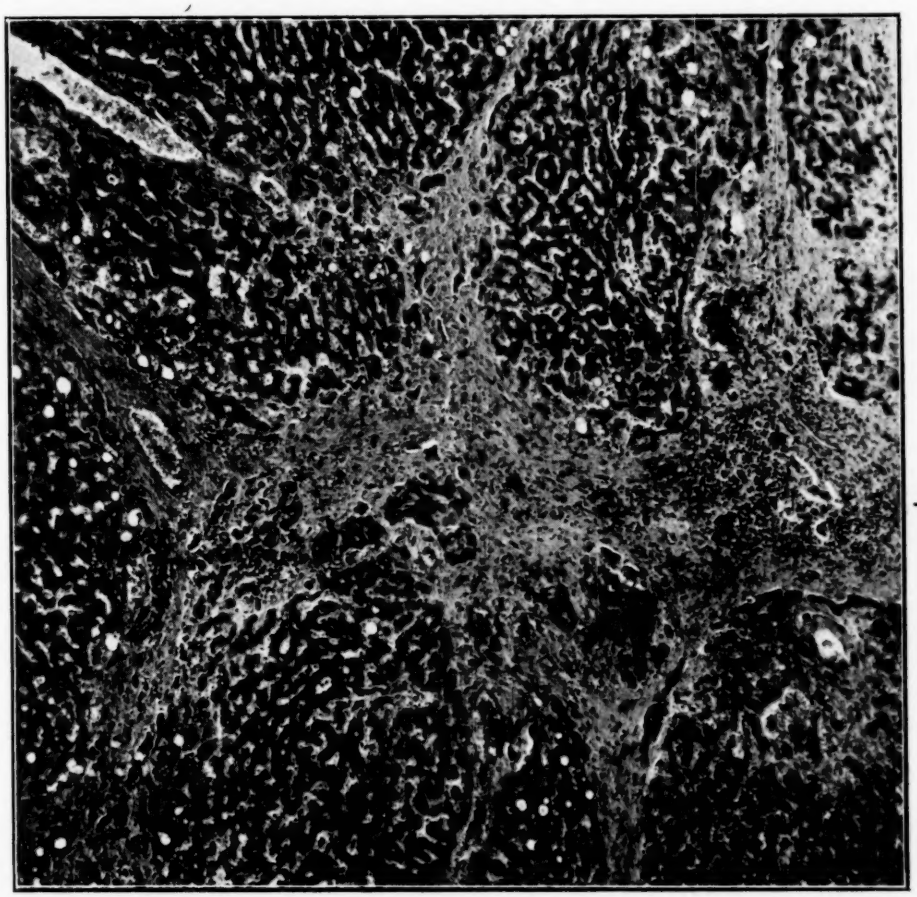

FIG. 3. Case 1. General low power view of part of liver whose destruction was minimal. Considerable orderly regeneration. Suggestion of active process at **X**

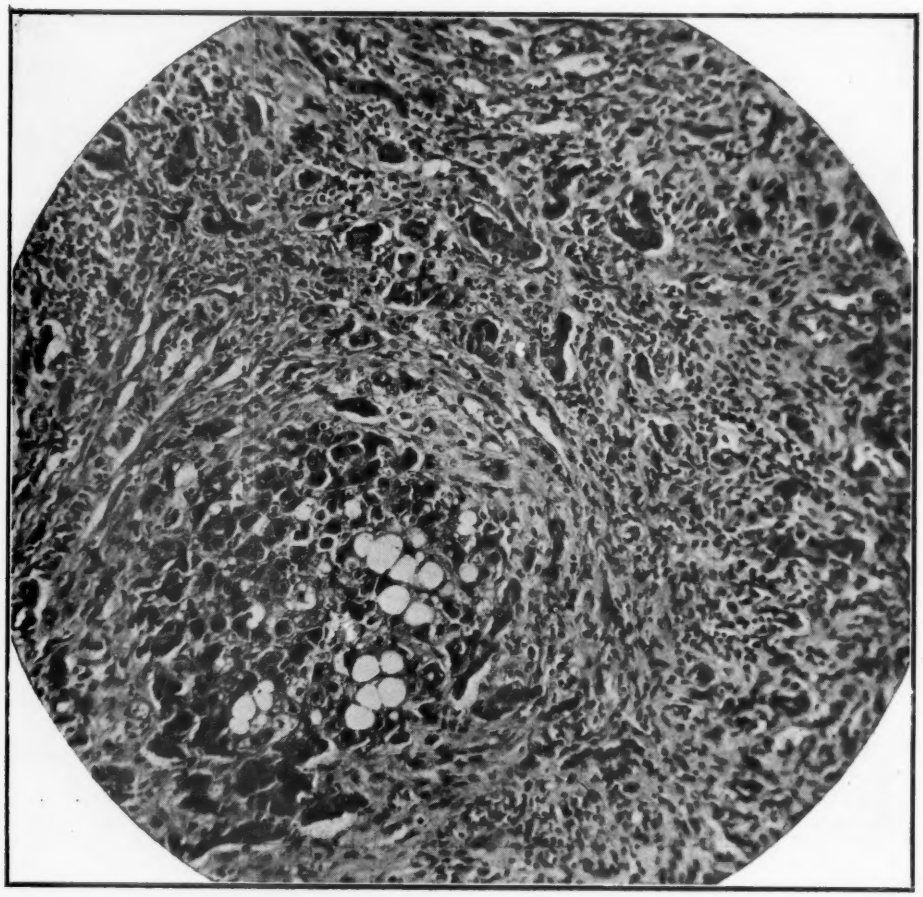

FIG. 4. Case 1. High power detail.

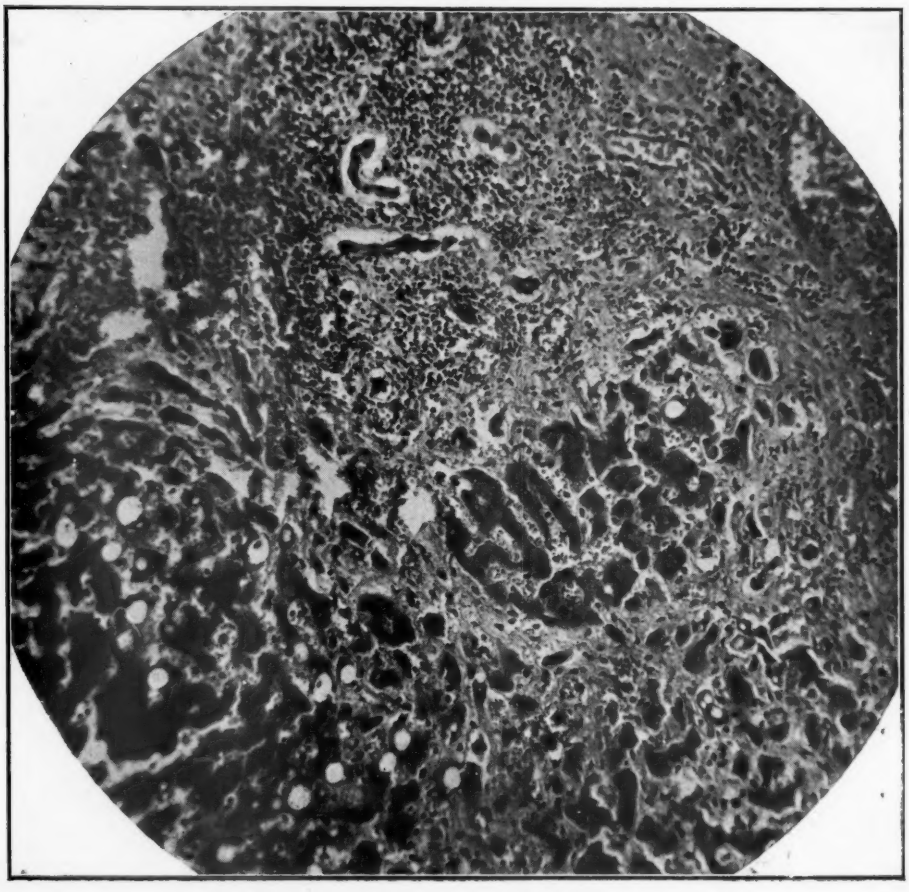

FIG. 5. Case 1. High power detail.

Case 2.—A girl, aged 2 years, was brought to the Royal Free Hospital with complaints of vomiting 8 days and jaundice 4 days before admission. The urine had been dark and the motions frequent, loose and grey. There was general irritability of temper. One day after the onset her left ear had started to discharge. A brother aged 7 years had had a slight attack of jaundice a few weeks previously and was now well. A careful enquiry subsequently discovered no other point that could be helpful in the ætiology, except that the child was very fond of bright-coloured sweets.

On admission the temperature was 99°, pulse 120, respirations 24. The child was irritable and cried incessantly. The jaundice was moderately deep; the liver was enlarged to 1½ inches below the costal margin in the mammary line. Stools were clay-coloured and urine dark with

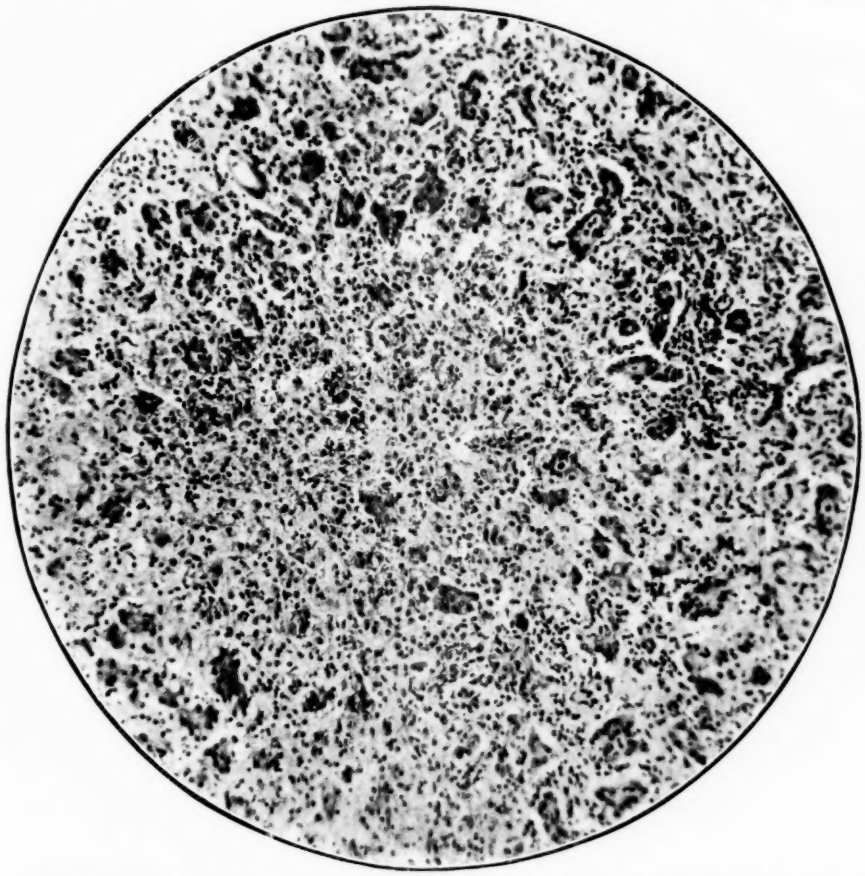

FIG. 6. Case 2. Showing complete destruction of parenchyma, and abundant new growth of bile ducts.

bile. The left ear was discharging freely. The case was diagnosed as one of catarrhal jaundice, probably epidemic, as her brother had had jaundice recently.

COURSE.—About 10 days after admission, however, it became evident that it was not running a straight forward course. The jaundice deepened, the liver became slightly more enlarged, the child was still excessively irritable; both ears were now discharging blood and pus. There was no pyrexia; indeed the temperature had been subnormal since the first day of admission. On the 21st day after illness she suddenly became rigid and semi-conscious, and exhibited Cheyne-Stokes breathing. Her blood count on this day was as follows: Red blood corpuscles 5,390,000 per c.mm., hæmoglobin 84 per cent., colour index ·8, white blood corpuscles 45,600 per c.mm., of which polymorphonuclears were 88·5 per cent., platelets 308,000. Fragility began at ·38 per cent. NaCl, finished at ·3 per cent.

The cerebro-spinal fluid was bile-stained, but otherwise normal and not under pressure. In the afternoon she had a hæmatemesis, followed by convulsions, coma and death.

Autopsy.—A well-nourished child with jaundice of skin and conjunctivæ, and some septic spots round about ears.

The dura mater was bile-stained and firmly adherent in the middle fossa. There was no evidence of extension of inflammation from the middle ears which both contained pus.

Liver slightly enlarged, pale and firm; on section it felt exceedingly tough like rubber. It was dirty yellow in colour with small punctate reddish areas, and the normal pattern was completely lost. The gall-bladder was hyperæmic and contained viscid white bile, the bile ducts were patent.

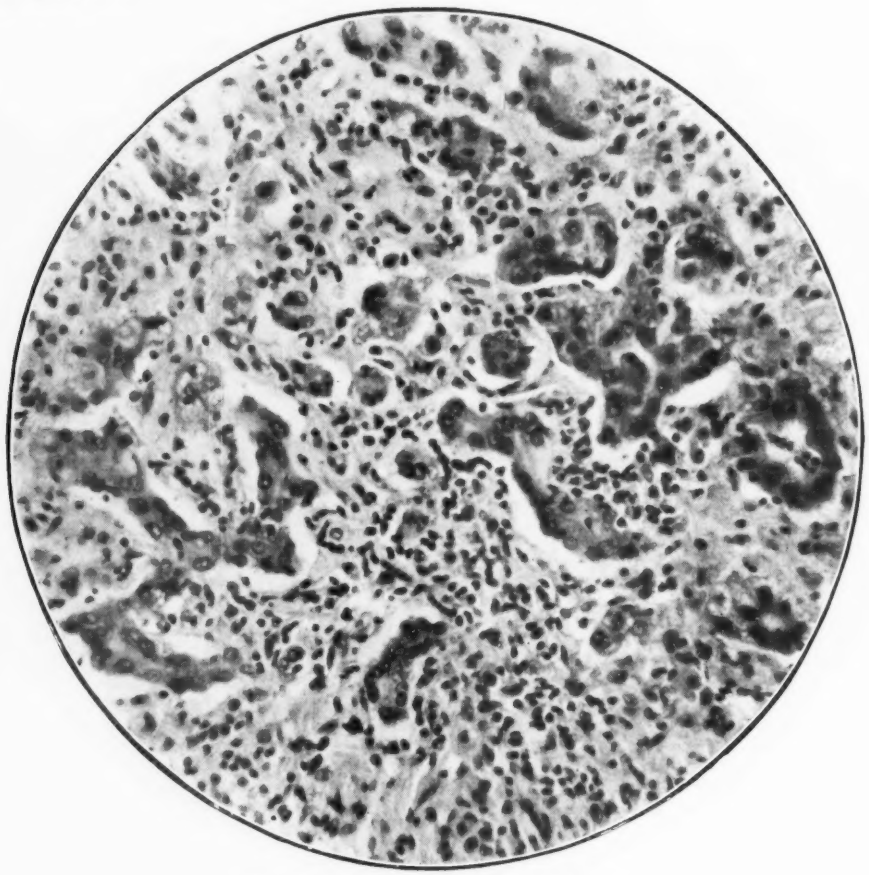

Fig. 7. Case 2. High power detail.

Heart and blood-vessels normal but bile-stained. Tonsils large with cheesy material in crypts. Lungs, interstitial emphysema, and some areas of collapse; pus in main bronchi. Stomach distended, containing tarry mucus. Upper part of small intestines contained altered blood. In the lower part of the ileum there were congestion and swelling of Peyer's patches. Ridges of mucous membrane in colon and rectum were reddened and there was some ulceration. Pancreas normal. Spleen showed some hyperplasia of the Malpighian bodies. The mesenteric glands were swollen and pink.

Microscopically, the sections showed complete destruction of the parenchyma of the liver, and its replacement by fibro-cellular tissue. New pseudo-bile canaliculi were present in large numbers but none of them had formed liver cells. There was no attempt at nodular hyperplasia and no sign of fatty degeneration. Under a high power ghosts of dead liver cells with faint granular protoplasm could be distinguished. This extensive destruction seemed to be evenly

distributed throughout the organ ; at no part did there appear to be any normal liver tissue left. These appearances were so similar to those produced by acute poisoning, such as by arsenic or trinitrotoluene, that tests were carried out for the detection of the former substance, but with a negative result.

Discussion.

Necrosis of the liver in young children, whether acute, sub-acute or chronic, is by no means a rare condition, but it is unusual to find a clear unequivocal cause, and only rarely can the destruction be traced to some definite poison, such as chloroform, arsenic or phosphorus.

The terminology used to describe these cases has been varied and often inappropriate. The word ' atrophy ' especially, as used in the terms acute and subacute yellow atrophy, is often incorrect as far as the bulk of the liver is concerned, and inadequate as applied to the liver cells, which have evidently been rapidly destroyed by some chemical or bacterial toxin. ' Necrosis ' is a better word. ' Yellow ' may indicate the fatty appearance such a liver occasionally presents, or may allude to the bile-staining, which is sometimes a prominent feature ; but profound degrees of necrosis may occur without either fatty deposits or retention of bile. The term ' acute ' is generally kept for those cases, allied to a similar condition in adults, where there is a fatal conclusion within a few days. ' Sub-acute ' is used for cases which last longer than a week, and these merge with a more long-standing condition which Marchand has termed ' nodular hyperplasia,' while these again are indefinitely divided from hepatic ' cirrhosis.' Another title which has some claim to recognition is that of ' toxic hepatitis.'

On reading the detailed accounts of many of the published cases of this kind, it becomes evident that although the morbid anatomy is becoming a well-recognized picture, or group of pictures, the pathogenesis remains obscure.

Morbid histology.—In children, at least, it is unusual to find the liver so completely and quickly overcome by a toxin that there has been no time for the tissues to make some form of reaction or attempt at repair. This, however, may have been of the slightest and only evident on microscopic examination ; on the other hand, if the child has lived for some weeks signs of repair may be obvious to the naked eye in the form of nodules of new liver tissue.

Necrosis is rarely evenly distributed. It occurs patchily, sometimes more in one lobe than another ; and in some cases considerable areas have been apparently so much less affected than the surrounding parts that they stand out as islands when the liver is examined at autopsy. At its worst the liver-cell destruction is complete, so complete that the cell columns have entirely disappeared, or at the most have faint ghostly outlines which may be detected in the stroma. The shrunken framework of the lobule remains, showing new fibro-cellular tissue taking the place of the parenchyma. In the most fulminating cases the lobular arrangement is completely lost and the section looks like a mere mass of granulation tissue, but more often the lobule is roughly defined by the abundant new formation of bile ducts which stand out sharply in the section with their deeply staining nuclei. These canaliculi do not con-

tain bile and have rarely made any connection with the remnants of liver tissue, but they are evidently a first step towards repair, and it has been demonstrated that they are capable of producing new liver cells if given time, and if other means of regeneration have failed. If any liver cells remain they are generally situated in the periphery of the lobule and may show mitotic division. It is from these that hyperplastic nodules develop in those cases which survive the first onslaught of the toxin. Such nodules of new liver tissue form themselves into cell-groups roughly mimicking the original lobular arrangement. They evidently function actively and are often deeply bile-stained, perhaps finding some difficulty at first in establishing a free communication with bile-ducts. That they are capable of carrying on liver functions adequately is proved by such cases as Whipple's[1 2], which was found by laparotomy to have had sub-acute yellow atrophy and recovered.

Fatty degeneration is much rarer than complete necrosis, except in cases of chloroform poisoning, but fat is often found in the newly formed cells of the regenerated nodules. Evidence of infection has been suggested by the presence in some cases of abundant leucocytes, and in others of enlarged glands in the portal fissure. An early stage of fibrosis is indicated by new peri-portal fibrous tissue which is often observed in the more protracted cases.

Pathogenesis.—It is interesting to read the accounts of acute and sub-acute liver atrophies in children, of which a great many cases have now been recorded, and to try and trace what was thought to be, or what might have been, the cause in each one. There is extraordinarily little unanimity of opinion about possible causes, and in individual cases there is more often a negative history than any suggestive fact of ætiology. It may be useful, nevertheless, to gather together such facts as we have in an attempt to elucidate a difficult problem.

Klopstock's[1] patient was a girl of 10 years who died of interstitial pneumonia, having had no symptoms of liver disease during life. The liver showed typical sub-acute yellow atrophy at autopsy.

In connection with this association it may be mentioned here that the present author has under her care a child of seven years old, who suffers from interstitial pneumonia, dating from a primary pneumonia at the age of two. This child has twice had acute exacerbations of the lung condition, accompanied by jaundice and enlarged liver; her lævulose test shows a decidedly faulty liver function. May she not be suffering from sub-acute hepatic necrosis?

McDonald and Milne[2] described a case in a girl aged 4, lasting 6 weeks. There was no known cause, but the child had an operation for adenoids 2 weeks previously, and had on two occasions suffered from jaundice, once at 2 years and once at $2\frac{3}{4}$ years. Nodular hyperplasia was found at autopsy. The two other cases of these authors, a girl aged 7 and a boy aged 7, showed no evidence of infective or other causes, either in the history or post-mortem findings.

Wilson and Goodpasture[3] described a case in a boy of 8 complicating cerebellar tumour. The two conditions were not necessarily connected, but a close connection has always been known to exist between liver and brain, as evidenced in the disease known as hepato-lenticular degeneration, and in

the deep bile-staining of the basal nuclei in cases of icterus gravis neonatorum, so that this association must not altogether be ignored.

Dingwall Fordyce's[4] patient, a girl aged 6 years and 11 months, had also had a previous attack of jaundice a year before admission. No cause was assigned, but it was recorded that she had left-sided paresis and a squint. However, nothing is mentioned of the central nervous system in the account of the autopsy.

Porter Parkinson's[5] case was a boy aged 3 years. A staphylococcal pyæmia was found in this case after an illness of 9 weeks.

Woolner's patient[6], a child aged 19 months, began mildly during an epidemic of jaundice, suddenly developed acute symptoms and died on the 12th day. There were enlarged glands at the portal fissure suggesting an infective origin. This case was similar to Case 2 recorded above, where the patient's brother had had catarrhal jaundice. In this connection it may be mentioned that Cockayne[11] and others have been convinced of the close connection between epidemic catarrhal jaundice and acute yellow atrophy, between which and sub-acute atrophy there is probably no difference but that of intensity.

C. E. Newman[7] has described several cases, chiefly in adults, and has pointed out the significance of the association of chloroform and sepsis in producing necrosis of the liver. One of his fatal cases had a staphylococcal peri-nephric abscess, the second was apparently a simple chloroform poisoning; but others that survived had both factors, sepsis and chloroform, in their ætiology.

B. Roman and D. W. Sherman[13] recorded a case in a boy of $8\frac{1}{2}$ months; duration about 9 days. There was an unusual amount of fatty degeneration in this case, otherwise it showed typical features of necrosis. No cause was assigned.

Griffiths[8], Hutchison and Paterson[9], Venn[10], and others have recorded cases but throw no light upon the cause.

Conclusions.

It appears that at present the utmost vagueness exists concerning the ætiology of acute and sub-acute hepatic necrosis in children.

Syphilis, although in its acute form it may produce considerable destruction of liver cells and abundance of fibrous tissue, does not quite fit into the histological picture as generally described, and moreover in the majority of reported cases has been definitely absent. Case 1 above showed no sign of syphilis at autopsy, and it can only be concluded that a positive Wassermann reaction after a provocative dose of arsenic is not always proof of syphilis.

Chloroform is a well-known liver poison and has been responsible for many deaths. The histological picture is one of extreme fatty degeneration, rather than of necrosis. Chloroform is not so widely used for anæsthesia as hitherto, and should never be used for septic surgery.

Arsenic, phosphorus and trinitrotoluene are unlikely factors in children's disease, although the first may be administered too freely in congenital syphilis. Other chemicals may play a part. It has been suggested by Professor Hadfield that the colouring matter of sweets may possibly be injurious.

The infective fevers are causes of hepatic necrosis; there do not seem to be any cases recorded in children.

Sepsis in some form or another appears from time to time in the records, and it is possible that it might have appeared oftener if a more detailed search had been made. There is scarcely ever any mention of the middle ears and mastoid antra in recorded autopsies; it would be interesting to know if they were examined.

Case 2 reported above had a purulent ear discharge; at autopsy pus was found in both middle ears. A boy of 8 years now under my care was admitted into the ward with enlarged liver, and jaundice which lasted eight weeks. It is now definitely clearing up since an offensive ear discharge has been treated by radical mastoid operation. It seems most probable that this child has some liver necrosis.

Absence of the mention of otorrhœa in the history means nothing, as so many parents class this as a minor malady, and think no more of taking the child to a doctor for treatment for this condition than for worms or running nose, both of which they consider inherent to childhood.

Whatever the cause, the comparative rarity of the disease would indicate that some other factor than a toxin must be at work in producing such catastrophic destruction in the liver. In the case of pregnant women it is assumed that the liver is already overburdened by the toxins of pregnancy; in the case of children and adolescents there is possibly some inborn hepatic weakness, but this is a purely theoretical assumption.

Investigation of the literature reveals the most painstaking and minute accounts of the morbid histology in every phase of liver necrosis, but a singular absence of careful enquiry into the history or associated morbid conditions. The symptomatology and morbid anatomy are now well-known, and it would appear that the investigation of further cases would be most usefully directed towards elucidating the cause of the disease.

I am particularly grateful to Professor Hadfield, Dr. Ross, and Dr. Temple Gray for their kindness in having sections prepared and photographed, and for their invaluable advice and expert opinion upon them.

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A CASE OF CONGENITAL HYPERTROPHIC PYLORIC STENOSIS

BY

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This case is reported because it presents some unusual features which, so far as I am aware, have not previously been encountered, namely, relapse of pyloric hypertrophy after operation, and the appearance of signs of congenital heart disease after blood transfusion.

Clinical report.

Eileen L., a female infant born normally at full term, was admitted at the age of 3 weeks to the East London Children's Hospital on May 19th, 1930.

She was the first child of healthy parents. Vomiting after each feed, with increasing constipation, had been noticed for 7 days previous to admission and had led to weaning and the usual rapid succession of proprietary foods. For 3 days constipation had been absolute.

On admission she was moderately well-nourished, and examination revealed marked visible gastric peristalsis and a definite tumour in the region of the pylorus. A water feed was forcibly ejected to a considerable distance. There was no other physical abnormality. It was specifically noted that the heart was normal in size and position, and the sounds clear. The turgor of the skin over the abdomen being poor, 125 c.cm. of combined solution[1] were administered subcutaneously; this was quickly absorbed, with improvement in her general condition. Feeds consisting of whole lactic acid milk (cultured) with 10 per cent. of mixed carbohydrates (six feeds of 75 c.cm. at 4-hourly intervals), and thickened by the addition of 20 per cent. barley flour were prescribed. Atropine was also administered, flushing of the skin being attained at 7 minims of a 1/1000 solution of atropine sulphate. Vomiting was unabated and operation was consequently deemed advisable. The weight at this time was 6 lb. 7 oz.

On May 21st, Mr. Acton Davis performed a Fredet-Rammstedt operation according to the technique recommended by Clopton and Hartmann[2]. The stomach was found to be dilated and the pyloric tumour was about ½-in. in length.

Three hours after her return to the ward the infant received 80 c.cm. of her father's blood intravenously and her condition, at no time very serious, improved considerably. The following day she received a second transfusion of 60 c.cm.

Some regurgitation of food occurred for the first few days, but this ceased entirely after five days, and there were 3 or 4 normal stools in every 24 hours. She was discharged on June 1st, 11 days after operation, apparently in good condition, though she had only gained 1 oz. in weight, which at this time was 6 lb. 8 oz.

On June 6th, 5 days after discharge, she was re-admitted with the history that vomiting had commenced after she had been home about 36 hours, and had increased in frequency till it was as bad as when she was originally admitted. The bowels, however, had continued to be regular. She had lost weight, being now only 6 lb. 3 oz. Examination still revealed visible gastric peristalsis but no tumour could be felt, perhaps because palpation was rendered difficult by the recent operation scar. Vomiting after a test feed was projectile. The heart and lungs, as before, showed no abnormality nor was there any evidence of parenteral infection to account for the vomiting. She was again given thickened feeds and atropine, and improved somewhat, weighing 6 lb. 12 oz. on June 15th. Stools averaged 4 daily and were normal in character.

Vomiting, however, persisted, and on this account Mr. Acton Davis decided to open the abdomen and inspect the pylorus, and on June 16th, i.e., 26 days after the first operation, this second operation was performed. The pylorus was found to have hypertrophied considerably, extending proximally as a new sphincter for about $\frac{1}{3}$-in. from the gastric end of the first incision, which was still clearly defined. The new pylorus was in every respect similar to the first, being pearly white in colour and cartilaginous in consistence.

Fig. 1 represents the tumour as found on May 21st, and the interrupted line indicates the incision then made. Fig. 2 shows the findings on June 16th, the continuous line indicating the incision made at the second operation.

The hypertrophied fibres were divided in their entire length and the abdomen closed in the usual manner. As the post-operative condition was excellent no supportive therapy was necessary. The patient gained weight steadily till July 6th, at which time she weighed 7 lb. 12 oz. and was taking six feeds of 120 c.cm. daily without any vomiting, and having from 3 to 4 normal stools in the 24 hours.

From this date she commenced to go downhill, losing weight, vomiting frequently, and having from 7 to 10 loose stools every day. On July 11th, both tympanic membranes were definitely reddened and bilateral myringotomy yielded sero-purulent fluid from each ear. Her general condition had become so poor that it was decided to give a blood transfusion, and on

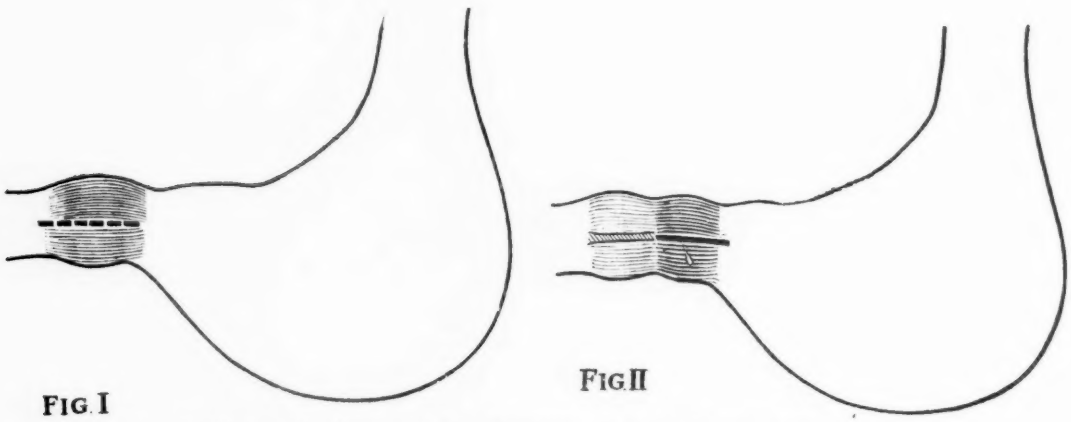

FIG. 1. Condition of pylorus and site of incision at the first operation.
FIG. 2. Condition of pylorus and site of incision at the second operation, 26 days later.

July 12th she received 100 c.cm. of her father's blood intravenously, followed some hours later by 175 c.cm. of 5 per cent. dextrose subcutaneously, and her general state was considerably improved thereby.

On July 14th examination of the chest revealed the presence of a loud harsh bruit all over the precordia, audible also over the back, with its maximum intensity just to the left of the left border of the sternum in the 4th intercostal space. There was no appreciable enlargement of the area of cardiac dullness, neither was there any cyanosis or dyspnœa. The bruit remained constant till her discharge on July 22nd at which time she was in excellent health and weighed 8½ lb.

Subsequently she attended the out-patient department of the hospital regularly every 2 or 3 weeks, and developed normally. By October 6th, she weighed 14 lb., and was taking 5 feeds of 210 c.cm. daily. At each attendance her cardiac status was carefully considered and it became apparent that the bruit was gradually disappearing, first becoming fainter, and then more localized, and finally on December 11th it was quite inaudible. At no time had she any symptoms, nor was her development in any way altered, her weight on December 11th, at the age of 8 months, being 18 lb. 1 oz. The average weight for this age is 18 lb. (Camerer). Subsequent repeated examination has failed to disclose any cardiac abnormality, both sounds being clear and of good quality.

Discussion.

The chief points of interest in this case are the development after operation of a second pyloric tumour on the proximal side of the first, and of a cardiac lesion following blood transfusion.

The first is probably to be explained by the escape of a minute ring of the fibres at the gastric end of the pylorus at the first operation. Mr. Acton Davis concurs in this opinion and thinks his original incision, while clearing the pyloro-duodenal junction adequately, did not extend sufficiently high at the gastric end. This may be accounted for by the relaxed condition of the stomach at the time of operation (lavage had immediately preceded it). Had the stomach been in a state of spasm the most proximal hypertrophied fibres would probably have stood out more clearly and the point at which it was safe to end the incision would have been more easily defined.

This ring of fibres may have led to spasm, which gradually increased until further hypertrophy, involving more and more fibres at the lower end of the stomach, resulted in the formation of the tumour found at the second operation.

The time elapsing before the development of the secondary tumour was almost identical with the time elapsing between birth and the original operation (23-26 days), and the second tumour was very nearly the same size as the first. Wollstein[3] performed autopsies on 25 infants who had been operated on for pyloric stenosis by the Fredet-Rammstedt method and who had died at varying times from 24 hours to 2 years after operation. She found that the scar on the pylorus gradually disappeared; after 10 days the scar was still wide, but after 25 days there was no depression appreciable though the scar was still visible, and the pylorus was but little firmer than normal.

Fredet[4] reported a case on which he had operated successfully 3 months previously and which had died of broncho-pneumonia. At autopsy there was no trace of the operative incision on the pylorus, but the pylorus still felt slightly thickened.

In the present case, after 25 days, the scar was still wide and the original pyloric tumour quite firm to the touch. Wollstein has shown that the hypertrophied muscle fibres take no part in the healing process, but that this occurs by contraction of fibrous connective tissue from the serous and submucous coats. The process of healing may have been delayed in the present case by the continued existence of a sphincter proximally.

With regard to the cardiac condition, it is probable that the third transfusion, which was the largest, in some way altered the intracardiac pressure so that a defect in the septum, most likely at the foramen ovale, previously so small as to give rise to no signs clinically, became enlarged to pathological proportions. With the continued growth of the infant this opening gradually re-closed.

In over 100 infants receiving one or more transfusions during the past year at the East London Children's Hospital this was the only case in which any such occurrence was noted. The average quantity of blood injected was 10 c.cm. per lb. of body weight, but in the present case this was increased

to 15 c.cm. per lb. There are two possible causes of the cardiac phenomenon here noted, first that the quantity was excessive, secondly that the rate of flow was too rapid. It would appear doubtful if the extra quantity of blood could greatly increase the intracardiac pressure ; there were no signs of right heart stress following the transfusion, and the long duration of the murmur is a further objection. With regard to the rate of flow, this was no faster than usual, the 100 c.cm. being injected in approximately 20 minutes. Robertson and Brown[4] stated that the rate of flow should not exceed 10 c.cm. per minute and they gave 120 c.cm. to a 6½-lb. pyloric stenosis baby who was 5 weeks old with strikingly good results. They had one fatality, in a 4-lb. baby, thought to be due to excessive speed of administration, but in that case death was instantaneous from rapid over-distension of the right heart.

It is unfortunate that in the present case blood counts were not made before and after transfusion, nor was a radiogram of the chest taken, for these might have given some help in elucidating the problem.

I am indebted to Mr. K. J. Acton Davis for permission to publish this case which was admitted under his care ; and to Dr. Leonard Findlay for his advice and suggestions.

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POST-ANGINAL SEPSIS
(Sepsis of Oro-Naso-Pharyngeal Origin)

BY

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The belief that the so-called common sore throat is of no serious consequence is fallacious: serious complications and death follow it sufficiently often to warrant a study of the complications of simple angina and their mode of evolution. It is true that in a great majority of cases, there is a restitutio ad integrum in a short time and that the patient is able to follow his usual mode of life in a few days; but it is equally true that in a certain number, after a period of from a few days up to from seven to eleven weeks after the angina has subsided, a group of symptoms, local and systemic (sepsis), develops which not only threatens life but may prove fatal. The evidence is cumulative and convincing. In many of these cases of post-anginal sepsis, either thrombosis (obturating or mural) or phlebitis of the internal jugular vein or its anastomosing branches was found at the operating table or on autopsy. In a number of instances of so-called idiopathic or cryptogenic sepsis, pathologists have demonstrated thrombosis of an internal jugular vein; it is deemed advisable now to explore the internal jugulars in cases of sepsis of unknown origin especially those following angina or any infection of the oro-naso-pharynx. This is considered good surgery in the field of the neck, just as it is considered advisable to explore a case of an acute surgical abdomen of unknown origin. This procedure is not only of theoretical value, for it has been carried out many times, and in cases in which the jugular and its anastomoses were ligated and excised early, the patients made rapid and complete recoveries. In many cases of sepsis following oro-naso-pharyngeal infection, where there is only phlebitis of the vein, the patients recover when the primary focus of infection is completely removed, even in the presence of metastases, without any operative procedures on the veins of the neck.

The subject deserves much greater attention than it has received. Apart from a few case reports there has not appeared a single comprehensive article on this subject in English. Most of the work has been accomplished in Germany, but the first who clearly and distinctly called attention to the correlation of primary angina and secondary sepsis associated with thrombosis of the internal jugular veins was Dr. Mosher of Boston.

Historical.

Quinsy and phlegmonous retro-pharyngitis were known to the ancients. Hippocrates not only referred to it but emphasized the presence of opisthotonos as one of its symptoms. He suggested that such abscesses should be opened with the finger if they were soft, and if not, an iron should be attached to the finger and the abscess opened with it.

Morrell Mackenzie stated that the first definite mention of abscess in the retro-pharyngeal region was made by Galen in the second century. He described a case with spontaneous rupture and stated that he had seen cases which resulted fatally.

Morgagni in the 18th century, gave a careful description; he cited a fatal case which ruptured into the trachea. In 1818, Abercrombie gave an accurate description of three cases in children. Henoch in 1851 gave credit to Fleming for first accurate description; the latter devised an instrument for opening these abscesses. In 1867 Gillette demonstrated the lymph nodes and vessels of the retro-pharyngeal space. In 1858 Bokai published a comprehensive manuscript on the subject. In 1859 Chassaignac ligated the carotid artery in a case of hæmorrhage following incision of retro-pharyngeal abscess. In 1897 Groosdinsky reported a case of extensive hæmorrhages into the skin, with staphylococci in the blood and suppurations of various organs traceable to an old retro-pharyngeal abscess. Tischulkin in 1897, reported fatal cases of bacterial sepsis as a result of tonsillar infections.

In 1914 Proskauer could collect only four cases of sepsis following peritonsillar abscess. Cases were also reported by Tollens (1902), H. J. Davis (1911), John W. Long (1912), H. Martin (1913) and Goodman (1917).

Mosher of Boston was the first to correlate the internal jugular vein thrombosis with the existence of the retro-pharyngeal abscess and wrote as follows :—

'Every case of peri-tonsillar or retro-pharyngeal abscess, active or quiescent, that has chills or shows a septic temperature, probably has a thrombosis of the internal jugular vein, and should be treated accordingly. When there has been a previous throat infection which has cleared up, but the patient develops a swelling of the side of the neck with a septic temperature and chills, the same condition prevails. Never let such patients die without uncovering the internal jugular vein and determining its condition.'

Subsequently Frænkel, Reye, Lewin and Rossle, Martens, Press, Melchin, Keppler and Clairmont Welte, Wessely, Hoandt, Uffenorde, Kelemen, Kunck, Zange, Claus, Waldapfel and Riecke have all written on the subject.

Portals of entry and their correlation.

There are many portals of entry in the naso-oro-pharynx which may give rise to foci of infection and which may terminate in jugular thrombosis and sepsis. The most important are (1) the Waledeyer ring of lymphoid tissue (palatine tonsils, pharyngeal tonsil, lingual, and lymphoid tissue in the fossa of Rosenmuller and elsewhere); (2) from the maxillæ, sinus, teeth, gums; (3) from the middle ear, mastoid and venous sinuses, and (4) from the salivary glands, especially the parotid. It is most important to know the anatomical relationships of these parts to one another, to understand the possible involvement of all of these portals of entry secondarily to involvement of any one of them. Thus, mastoiditis may follow retro-pharyngeal abscess, and retro-pharyngeal abscess may follow mastoiditis by retrograde thrombosis; suppurative parotitis frequently follows otitis media purulenta and infection in the oro-naso-pharynx. Infection of the Waldeyer ring leads to para-sinusitis and this to otitis media. Ludwig's angina, peri-tonsillar abscess, retro-pharyngeal abscess and para-pharyngeal abscess are nature's reaction to a local infection, depending on the localization of the infection and on the peculiarity of anatomic structure of the parts involved. On final analysis,

it is all a matter of lymphatic drainage of different areas ; depending on the area involved we may have any one or all of the conditions enumerated. They are nature's second line of defence. If the infection be located in the floor of the mouth or gums, we have the possible development of Ludwig's angina ; if in the posterior naso-pharynx we may have a retro-pharyngeal abscess ; if in in the area of the tonsils, we may have peri-tonsillar abscess or abscess in the tonsil ; and the last two may spread to the para-pharyngeal space.

Besides the suppurative process which may occur in these parts we may have two other conditions, depending on the severity of the infection and the resistance of the patient. In many cases, there is only hypertrophy of regional glands without suppuration, and often these masses are needlessly incised ; thus, in many cases of acute infection of the adenoids, the retro-pharyngeal glands may be very much enlarged, and may produce a clinical picture not unlike that of meningitis, and yet there may be complete resolution without suppuration if the primary focus of infection in the posterior nares be promptly and properly met by suction or washing, or by emptying pockets of pus in the folds of adenoid tissue by manipulation with the finger in the posterior naso-pharynx.

On the other hand, in a case of severe infection of these parts in an individual with diminished resistance we may have a condition simulating a phlegmon of the throat in which all parts are equally affected, and there is a brawny induration of all anatomic parts of the throat and neck. This is a very serious condition and almost always proves fatal unless relieved by prompt surgery.

The evolution of sepsis.

To understand the evolution of sepsis in these cases of infection in the oro-naso-pharynx we must have a clear understanding of what is meant by retrograde thrombo-phlebitis and sepsis.

The process of retrograde thrombo-phlebitis implies the inflammation of a vein and its occlusion by a thrombus, which progresses in a direction opposite to the blood current. Thus the small venules of the tonsil may become thrombosed and this process may extend to the jugular vein and the venous sinuses of the head.

By sepsis is meant the invasion of the blood stream by bacteria and their lodgement in tissues (reticulo-endothelial system) where they are either destroyed with the liberation or formation of a toxin, or where they form metastases. The mere presence of bacteria in the blood does not constitute sepsis ; it simply implies the presence of a bacteriæmia. This occurs at the onset of many infectious diseases.

Bacteria do not long survive nor increase in number in the blood except in pre-agonal conditions. The type of fever curve seen in sepsis depends on the number of bacteria and the periodicity of invasion of the blood stream ; a chill usually occurs one to two hours after an invasion of many bacteria in the blood and is the result of the reaction between them and the tissues with the formation and liberation of toxin in the blood. The bacteria do not live much longer than 15 to 30 minutes in the blood after invasion.

For the occurrence of sepsis the bacteria must be in the blood vessels. In lymphangitis the blood is usually sterile. It is only when lymphoid tissues break down and the micro-organisms gain entrance into the blood stream that sepsis results : as long as the lymphatic

and lymph glands stem the tide of infection and protect the blood stream, the infection is local and there is no sepsis.

The bacteria are destroyed in the parenchymatous organs through phagocytosis not by the leucocytes, but by the fixed tissue cells of the reticulo-endothelial system (the histiocytes). It is the cellular and not the humoral forces of resistance which are called upon mainly to destroy micro-organisms. For every 1,000 colonies that are found in 1 c.cm. of venous blood, there are probably 500 millions of bacteria in circulation. In a healthy individual they disappear within 15 minutes from the blood. Therefore it is not their appearance in the blood but their deposition in the tissues and in the peritoneum that is dangerous. Human blood in vitro also destroys bacteria; one hundred bacteria in 5 c.cm. of blood are either destroyed or become inactive. Every infectious fever is brought about by invasion of the blood or lymph by micro-organisms, and the height of the temperature depends on their number and activity. A sudden inflow of bacteria into the blood stream is followed within one to two hours by a chill and high fever; the duration and variability of temperature depend on the duration of the bacterio-lymph and on the bacteriæmia. A drop in temperature in these cases indicates cessation of inflow or conquest of bacteria. The fever curve is a true picture of the number, of the virulence and the duration of blood invasion by bacteria. A local infection, however extensive, does not give rise to fever when few or no bacteria make their way into the blood stream, even though virulent bacteria are present in the focus of infection. The mere presence of bacteria in the lymph or blood does not produce fever; this occurs only when there is liberated an endotoxin as a result of their destruction in the tissues. In every case of sepsis a focus of infection is present (though not always demonstrable). The most common foci of infection are phlebitis, thrombo-phlebitis or lymphangitis. In lymphangitis there are few or no bacteria in the blood. A suppurating lymphatic gland is only a local infection as long as it does not break down into a vein; when this occurs it becomes a septic focus. Contrariwise a phlebitis is always a septic focus.

In many cases of post-anginal sepsis there is only found a thrombosis of the retro-tonsillar veins. Thrombosis of the jugulars is found only in a minority of the cases. In the majority of cases there is a small abscess formation behind the tonsils; in a smaller number of cases there is thrombosis of small venous radicles. Abscess formation frequently occurs without thrombosis, but thrombosis without abscess formation practically never occurs.

In sepsis of post-anginal origin there is a considerable difference of opinion as to mode of involvement of the jugular vein where it becomes thrombosed. One group of observers believes that there is a direct extension of the thrombosis from the smallest venules of the tonsils to the jugular by its anastomosing branches; another group believes that the infections spread by lymphatics and eventually involve the veins. This discussion is of purely academic interest. Eventually there must be bacteriæmia if sepsis is to result; whether the blood stream becomes primarily involved through the smallest venules or secondarily by the breaking through of a suppurating lymph gland is of no significance for the evolution of sepsis; the bacteria must find their way into the blood stream eventually.

It is also important to differentiate between the portal of entry and the focus of infection. In many cases they are not identical. This knowledge is essential for the proper treatment. The tonsil may be the portal of entry; the focus of infection may be a peri-tonsillar abscess. In many cases the portal of entry and the focus of infection are identical. The removal of the tonsils in a certain number of cases of sepsis without accompanying peri-tonsillar abscess has brought about immediate relief and prompt recovery from the sepsis.

Anatomical.

To understand the relationship of peri-tonsillar abscess to abscesses in the retro-pharyngeal and para-pharyngeal spaces, one has to be familiar with the anatomical relationship of these spaces.

A peri-tonsillar abscess may break through into the retro-pharyngeal space, and perforate the posterior wall of the pharynx as a retro-pharyngeal abscess.

Behind the tonsil is a peri-tonsillar space which is bounded posteriorly by the posterior pharyngeal fascia; between the posterior pharyngeal fascia and the prevertebral fascia is the retro-pharyngeal space, in which are located glands which are the seat of suppuration in retro-pharyngeal abscess. Lateral to the peri-tonsillar space and separated from it by pharyngeal fascia is the para-pharyngeal space; this space is bounded laterally by the parotid gland and within this space course the 9th, 10th and 11th nerves, the ganglion of the superior cervical sympathetic, the internal carotid artery; adjacent to the parotid gland, the external carotid artery makes its course. In the lateral posterior corner of this space, the internal jugular vein may be seen. In these spaces are located the lymphatic glands which drain the Eustachian tube, posterior nose, middle ear and roof of pharynx. Many of these glands are not found in adults; this explains the more frequent enlargement of deep jugular lateral lymph glands in children. The deep cervical glands course along the internal jugular vein and the internal carotid artery. These drain the mouth, tonsils, palate, pharynx, tongue, nasal fossæ, interior of skull, deep parts of head and neck, and when they suppurate they produce para-pharyngeal abscess.

In 1921 Kaufman pointed out that aspiration pneumonia may follow the spontaneous rupture of these abscesses. He thought that it was possible for mediastinitis, pleurisy and œdema of the larynx to develop as a result of these infections; and clearly stated that small venous branches or the jugular its elfmay be the seat of thrombosis and give rise to pyæmia, the blood in such cases becoming infected and giving rise to metastases.

Symptomatology.

The symptomatology may be divided into several stages.

(1) Local symptoms due to primary infection (angina, Waldeyer ring inflammation, maxillary osteomyelitis, sinusitis, infection of teeth, infection of gums or floor of mouth, otitis, mastoiditis or venous sinus involvement, salivary gland involvement).

(2) Latent period.

(3) Symptoms due to involvement of neighbouring lymphatic glands, or to extension of the suppurative process within the immediate neighbourhood of portal or entrance of infection. (a) Simple hypertrophy of regional glands: abscess of regional glands; (b) hypertrophy of retro-pharyngeal glands: abscess of retro-pharyngeal glands; (c) peri-tonsillar abscess; (d) Ludwig's angina; (e) para-pharyngeal abscess; (f) phlegmon; (g) abscess extension by contiguity (gravitation abscess).

(4) Symptoms of sepsis: (a) with phlebitis of veins; (b) with thrombosis of veins; (c) without phlebitis and without thrombosis (?).

(5) Symptoms due to metastases.

(6) Symptoms due to retrograde thrombo-phlebitis: (a) by continuity; (b) by embolism.

(7) Symptoms due to pressure.

(8) Symptoms due to erosion.

(9) Local symptoms.

(1) **Local symptoms.**—The earliest symptoms are those of the primary infection. This may have its inception in any of the structures of the oro-naso-pharynx. The severity of the primary infection has no definite relationship to subsequent development of sepsis ; cases severe and stormy at onset may make uneventful recovery without sepsis, and seemingly mild cases after apparent recovery may terminate fatally with septic manifestations. Apart from our general knowledge of the factors on which immunity and resistance to infection depend, the evolution of sepsis in these cases is not clear. The term post-anginal sepsis is a misnomer ; the infection may originate from lymphoid tissue (Waldeyer ring—lingual tonsil—palatine tonsils, pharyngeal tonsil, adenoids) ; from anywhere in the naso-pharynx ; from the bony maxillæ, teeth, and parasinuses ; from the gums and from all structures at the floor of the mouth ; from the middle ear, Eustachian tube, mastoid and venous sinuses, and from the salivary glands.

(2) **Latent period.**—In those cases in which sepsis develops there is a latent period which varies from one to four days to from three to seven weeks following the initial infection. In this period many of the local manifestations of infection disappear, so that examination by inspection of local conditions is usually negative. Valuable information, however, may be gained by bimanual palpation, as deep abscesses and induration may only be discovered by this method of examination. Where there is a difference in the appearance in the parts affected on both sides, the part which looks the more pathological may not be the one responsible for the sepsis. The apparently normal looking tonsil or tonsillar area has been found on more than one occasion to be responsible for the sepsis, whereas the diseased looking area was not the primary cause of the sepsis.

(3) **Extension symptoms.**—The lymphoid tissue and lymph glands which drain the oro-naso-pharynx are the second line of defence against blood infections. It is natural to expect hypertrophy of the glands which drain the areas involved. Hypertrophy does not necessarily mean suppuration. In the majority of cases there is complete resolution without suppuration when the primary focus of infection is eradicated and properly met. In the minority of cases this hypertrophy goes on to suppuration. If the infection be mild and is properly met there is only hypertrophy followed by complete resolution. If the infection be of severe type or the patient of lowered resistance, the infection assumes the character of a phlegmon. This involves all tissues ; induration and œdema of local parts are marked ; there are severe general symptoms, and unless the condition receives prompt and proper surgical attention the outcome is fatal in a very few days.

The seat of the primary infection determines the location of the second line of defence ; it is all a matter of lymphatic drainage. Depending on which locality is drained we have the following conditions to consider :—retro-pharyngeal abscess ; peri-tonsillar abscess ; Ludwig's angina ; para-pharyngeal abscess ; abscesses which extend by gravity to structures below along lines of natural cleavage to the mediastinum,

RETRO-PHARYNGEAL ABSCESS.—This is a condition found almost exclusively in infancy and early childhood ; it is very rarely found in adult life ; about 75 per cent. of these patients are under one year of age. Its ætiological relationship to caries of vertebræ and foreign bodies is well understood, and will not be considered here. It may follow infection in the nose, middle ears, sinuses, teeth, mouth, pharynx and larynx.

The great susceptibility in infants is probably due to the presence of a larger number of glands in the post-pharyngeal space (3 to 10 or more) ; in adults there are rarely found more than one or two. The retro-pharyngeal glands receive afferent lymphatic vessels from para-sinuses, nasal fossæ, pharynx and larynx. These glands send efferent vessels to the internal jugular group of the superior deep cervical chain.

The vertebral, pharyngeal and para-vertebral glands are intimately associated with the adenoid vegetations. The symptoms are practically the same as those of peri-tonsillar abscess, except that the course is more prolonged and the pain is less. In children the onset is insidious and the symptoms are due to interference with deglutition, respiration and with speech (dysphagia, dyspnœa, rhinolalia). Respiratory interference is more common in children, because the larynx is located at least one vertebra higher than in adults and this in spite of the fact that the neck is proportionately longer. The cry is peculiar (cri de canard).

An irritable cough is usually present ; and croup due to reflex spasm has been often mistaken for diphtheria. When the abscess assumes large proportions pressure symptoms develop, which if not relieved may prove immediately fatal. The diagnosis is often made on palpation when inspection is not satisfactory ; if a definite fluctuating mass be felt, it should be immediately opened ; otherwise there is danger of spontaneous rupture (due to manipulation) with fatal termination. A number of cases have been recorded, who succumbed suddenly after manipulation. Before opening an abscess it is most important to be sure that we are not dealing with an aneurysm. A colleague opened one with fatal outcome, when the aneurysm was mistaken for a retro-pharyngeal abscess. When opening these abscesses, a mouth gag should not be used. In the great majority of cases there is but little elevation of temperature ; in a small number it may be as high as 104-105° F. It is in these cases that the cervical glands are particularly large, though they are enlarged to some extent in most cases ; the cocking of the head on the contrary is most apt to be seen when the retro-pharyngeal glands are especially enlarged.

PERI-TONSILLAR ABSCESS.—This is rarely met in children, compared with the frequency of retro-pharyngeal abscess ; but, it is not as rare as the literature would indicate. We have had three cases of peri-tonsillar abscesses in children under three years of age at one time. In the great majority of cases the abscess is antero-superior to the tonsil. In about 7 to 10 per cent. of cases it is bilateral. The symptoms are much the same as those of retro-pharyngeal abscess. Pain, fever, chill, dysphagia, dyspnœa, offensive breath, swollen lymphatic glands at angle of jaw, œdema of uvula (not seen in retro-

pharyngeal abscess,) which is deviated to normal side, and œdema of the soft palate.

PARA-PHARYNGEAL ABSCESS.—The para-pharyngeal space may become involved primarily, or may be the seat of suppuration secondary to peritonsillar abscess or retro-pharyngeal abscess. When suppuration occurs in this space, internal incision does not usually relieve the condition and external operation becomes necessary. Broca in 1903, pointed out that almost all acute para-pharyngeal abscesses are adeno-phlegmons and involve the chain of glands along the carotid sheath, as distinguished from those in front of the pre-vertebral muscles. These drain the mouth, tonsils, palate, pharynx, tongue, nasal fossæ, interior of the skull and deep parts of head and neck.

LUDWIG'S ANGINA.—Ludwig's angina is a phlegmonous process arising from infections within the floor of the mouth localized in a definite anatomic space. This space is secured by boundaries and has as its floor, the mylohyoid muscle ; as its lateral walls, the bodies of the mandible ; as its posterior wall, the muscles which unite to form the base of the tongue and the deep part of the maxillary glands ; and as its roof, the tongue and the muscles covering the floor of the mouth. The origin of the infections which develop into Ludwig's angina is within the lower gingival borders, usually around the teeth and the floor of the mouth. There is proof against the theory that the primary infection is in the submaxillary space. This area is drained by deep cervical glands alongside the carotid sheath.

GRAVITY ABSCESSES.—These abscesses in the throat may rupture spontaneously and drain into the pharynx ; they may burrow behind large vessels and the sterno-mastoid muscle and point in the posterior lateral triangle of the neck ; they may rupture through the fascia and point anterior to the muscle in the anterior triangle ; they may gravitate to lower parts of neck, under the clavicle and in the axilla (Pott's disease) ; they may travel downward behind the œsophagus into the posterior mediastinum.

MAXILLARY SEPSIS IN INFANTS.—There have been reported about 32 cases of sepsis in infants following acute osteo-myelitis of the superior maxilla. In the majority of cases it has been mistaken for sinus disease. About 25 per cent. of cases die. It affects especially new born or very young infants. The infant suddenly becomes ill with fever and marked prostration ; there are swelling and redness about the tissue of one eye. These are followed or accompanied by a purulent, unilateral nasal discharge, by swelling and softening of the alveolar border of superior maxilla on the affected side, and by pointing and the formation of abscesses on the hard palate, the alveolar border and often on the face between the eyes and nose. Sequestra and frequently small teeth are discharged from these sinuses. Such cases show high irregular fever ; the blood culture is positive. The majority recover ; others develop metastatic abscesses and succumb.

(4) Symptoms of sepsis.—These are so well known that we need not dwell long on this point. Fever is the outstanding symptom. It may be continuous or intermittent ; and is usually associated with chills which are present

in one-half the cases of sepsis. Chills at the onset of the initial infection are of no significance ; but when they reappear after the latent period, great importance must be attached to them, especially if they are repeated. The pulse is rapid, soft and variable ; the skin is highly coloured or dusky to cyanotic ; the spleen and the liver are enlarged ; diarrhœa is frequent ; vomiting is not often present. Drowsiness is present. The blood culture is positive in half the cases ; a negative culture, is of no significance. The urine shows evidence of toxic irritation and a few red blood cells are usually found at every examination. The white blood cells are increased in number ; the polymorphonuclear count is high. In adults, a state of euphoria has been noted many times.

In these cases of sepsis, there is primarily a phlebitis of a vein (mural thrombus). The pathological process may not go on beyond this and the patient may get well even in the presence of metastases, with surgical treatment to the local condition.

In a small number of cases, the phlebitis goes on to complete thrombosis, with the formation of an obturating thrombus. These cases must be recognized early and the condition must be properly met surgically if they are to be saved.

In another group of cases, the so-called fulminating type, there is no abscess formation, there is no phlebitis and there is no external cervical swelling. The body is overcome by a very rapidly advancing blood infection, and the condition proves fatal in three or four days.

(5) **Metastases.**—The local symptoms and signs may be so insignificant that the condition may be entirely overlooked, were it not for the appearance of metastases. Metastatic involvement of lung (multiple abscesses) is perhaps the most common metastatic lesion. The signs in the lungs are not clear cut and are often missed without X-ray examination of the chest. Empyema and pleurisy are frequent metastatic lesions. Metastatic lesions have been recorded in the endocardium, joints, kidneys, central nervous system, genital organs, eye, ear, bone-marrow, spleen and liver, skin, appendix, peritoneum, subphrenic abscess. These give symptoms peculiar to the organ involved.

The streptococcus causes metastases usually in the lungs, pleuræ, endocardium and joints, and these lesions suppurate in 25 per cent. of cases. The staphylococcus produces purulent metastases in 45 per cent. of the cases. The pneumococcus usually produces purulent meningitis and endocarditis.

(6) **Retrograde thrombo-phlebitis.**—Symptoms due to retrograde thrombophlebitis are usually due to thrombosis of the internal jugular vein and the venous sinuses which directly or indirectly open into it. Thus we may have thrombosis of lateral, cavernous and petrosal sinuses ; in fact, we have once seen all the venous sinuses of the head become thrombosed. Basilar and general meningitis have been recorded many times ; this may take place by direct extension from the para-pharyngeal space or by continuity or by embolism through the venous sinuses. Abscess of the brain and encephalitis have also been noted as complications of this condition.

Wessely in experimental injections of tonsils with Indian ink, proved that there is a direct channel from the tonsils into the para-pharynx, and from there to the base of the brain to foramen ovale. He thus explains the spread of infection to the brain and meninges in these cases by direct extension. He believes that the infection may spread to the brain through the loose tissue in the para-pharyngeal space, through venous anastomoses, or by both routes.

The first case with cerebral complications was reported by Stanislaus v. Stein (Moscow) in 1885. He reported a case of acute phlegmonous pharyngitis, complicated by purulent meningitis. Other cases with meningeal complications have been recorded by Tollen (1903), cavernous sinus thrombosis—purulent basilar meningitis; Jacques and Lucien (1908) cavernous sinus thrombosis; Kandler (1907) abscess of brain; Proskauer (1914) purulent hæmorrhagic inflammation of dura and circumscribed lepto-meningitis; Fall (1919) abscess followed by osteo-myelitis, necrosing osteo-myelitis and meningitis; Höstorn (1920) cavernous sinus thrombosis and basilar meningitis; Beck (1914) suppurative meningitis, extra-dural abscess.

(7) **Pressure symptoms.**—The symptoms which may be expected as a result of pressure in this locality become clear if we refer to the anatomy of the parts. In the neighbourhood of the para-pharyngeal space are the internal jugular vein, the 9th, 10th and 11th nerves, the ganglion of superior cervical sympathetic, the hypoglossal nerve; and the alveolar and facial nerves are in close proximity to the parotid, which not infrequently becomes involved in the abscess formation. Hence symptoms of vagus irritation, and irritation of the 9th and 11th nerves may be found. Pressure may be exerted on larynx, œsophagus, thyroid, trachea, lung; therefore difficulty in swallowing, voice changes, hoarseness, dyspnœa (air-hunger) may result. A symptom often present in these cases is opisthotonos which leads to a mistaken diagnosis of meningitis. This is probably due to irritation of spinal nerves by enlargement of, or abscess in, the retro-pharyngeal glands.

(8) **Erosion symptoms.**—Symptoms may arise suddenly from erosion of vessels or from rupture of an abscess into various organs, as ear, pharynx, larynx, lung, mediastinum, or intra-cranially through the internal auditory canal. When erosion of blood vessels occurs, it usually involves the internal carotid artery or branches of the external carotid artery (lingual, facial, or ascending pharyngeal).

(9) **Local symptoms.**—These may play only a secondary role in the establishment of a correct diagnosis. In the throat there may be but slight evidence of present or past disease. One side of the throat may appear more nearly normal than the other, and yet may be the cause of jugular thrombosis. In the cases in which retro-pharyngeal or peri-tonsillar abscesses or Ludwig's angina are present, the local appearances are quite characteristic. In the great majority of cases, there is external swelling of the neck (lymphatic glandular enlargement) or brawny induration as in Ludwig's angina; deep pain at angle of jaw is usually present and may be elicited on pressure; in the neck an indurated strand following the anterior border of the sterno-mastoid muscle may be felt. In many cases trismus is marked. The odour of the mouth is foul. An exudate on the tonsils and fauces may be present which makes it imperative to differentiate this condition from acute leukæmia, agranulocytic angina, monocytic angina, Vincent's angina and diphtheria.

X-ray examination.

An X-ray examination should always be made to rule out foreign body, caries of vertebræ and mastoiditis. In not a few cases an abscess which was not suspected or which could not be seen or felt, was discovered by the use of the X-ray.

Bacteriology.

In many cases the anærobic streptococcus putrificus was isolated from the local abscess and from the blood. Many other organisms have been responsible for the condition; streptococcus hæmolyticus, streptococcus viridans with influenza bacillus, staphylococcus albus, etc. S. putrificus especially causes a foul local odour, a rapid course, and metastases, preferably in the lung. The ærobic bacteria metastatize preferably in the joints, muscles, skin, and not so frequently in the lung; the course is not so stormy though it may last for weeks; these cases usually get well when internal jugular is ligated.

The anærobic bacteria are more apt to invade venous channels, whereas the ærobic first invade the lymphatics and then the blood vessels.

Frequency and prognosis.

Post-anginal sepsis is far more frequent than the case reports and the literature suggest. We have had four cases of the condition in children at the hospital at one time. It is far more frequent in children than the literature indicates. We have had 10 cases (with three deaths) in children under 10 years of age in less than 18 months.

One hundred and thirty-seven cases of post-anginal sepsis were collected by Uffenorde in 1928. Of these 87 were males and 50 females, and 3 were under 10 years of age, the youngest being 5 years. In mild cases the condition may last only 3–8 days after the latent period. In fulminating cases, without visible pathology, and in phlegmonous cases with much induration and œdema, the outcome may be fatal in 3-4 days. In the majority of cases the course lasts from 8-21 days or longer, depending on the number and severity of metastases.

Most authors have found the lesions more frequently on the left than on the right side. Waldapfel in 43 cases noted that the lesions were on the right side in 13 cases, on the left in 20 cases, and bilateral in 10 cases.

Mortality.—In 137 cases collected by Uffenorde, only 40 recovered or were cured by operation. Reye reported 12 deaths in 17 cases; Waldapfel 25 deaths in 43 cases; Claus 14 deaths in 28 cases. In Waldapfel's series, of the 25 fatal cases, 17 were operated on and 8 were not; of the 18 surviving cases, 15 were operated on, and 3 were not.

Diagnosis.

The diagnosis of post-oro-naso-pharyngeal sepsis rests on the following points:—

(1). The history is of utmost importance. In almost every case there is a previous history of angina, tonsillitis, tooth infection, sinus disease, otitis, parotitis, gingivitis, adenoiditis, etc.

(2). In the majority of cases there is a latent period following the primary infection, varying from one day to one month.

(3). The sudden onset of septic symptoms with recurrent chills and in many cases positive blood culture.

(4). In the great majority of cases external swelling of the neck is present.

(5). The presence of metastases in lung, pleura, joints, heart, meninges, venous sinuses, etc.

(6). The local lesion may appear fairly normal or show but slight disease. In cases where the lesions are not apparent on inspection, information can be obtained by bimanual palpation and by X-ray examination. In the majority of cases there is evidence of peri-tonsillar, retro-pharyngeal or para-pharyngeal abscess.

(7). Exploratory operation and inspection of the internal jugular vein is indicated in every case presenting the above symptoms which has a positive blood culture and presents a cord-like thickening along the sterno-cleido-mastoid muscle.

DIFFERENTIAL DIAGNOSIS.—In every case of foul smelling angina we must think of acute leukæmia, agranulocytic angina, monocytic angina, Vincent-Plaut's angina, and diphtheria.

In those cases in which there is a grey foul-smelling exudate on tonsils and pharyngeal walls it is safer to administer antitoxin before the report of the culture is known.

In leukæmia, especially in acute lymphatic type, there is often a necrozing infiltration of the tonsils with foul odour. The blood when characteristic usually renders the diagnosis simple ; but in many cases, the blood picture may be aleukæmic and the differential count not characteristic. In these cases there may be general adenopathy, symptomatic purpura, negative blood cultures, much greater splenic and hepatic enlargement ; the course is longer ; and biopsy of an affected gland will establish a definite diagnosis.

Agranulocytic angina is rare in children ; although instances in children have been recorded by Chrisloff, Weiss, and Dwyer and Helwig. In this condition there is a necrozing inflammation of gums, tonsils and mucous membrane of the mouth and other mucous membranes (stomach, intestines, vulva). In association with this there is a leukopenia with a marked diminution to total disappearance of polymorphonuclears. There is little if any enlargement of the regional lymph nodes, and in about half the cases, icterus is present. This condition is to be differentiated from a clinical and blood picture which terminates leukæmia and sepsis. As favourable results have been reported by Friedemann with X-ray tests, cases should be given this therapeutic test.

Infectious mononucleosis, described in 1920 by Sprint and Evans is a self-limited disease in which there is a natural tendency to recovery within 2 to 3 weeks ; it is characterized by a transient lymphocytosis, fever, enlargement of the spleen and lymph glands. The tonsils may be covered with a diphtheria-like membrane ; they have no general symptoms of sepsis.

In Vincent's angina, the ulcerations and the finding of the organisms (spirilla and bacilli) in pure culture is diagnostic. In all throat conditions Vincent's spirilla may be found in conjunction with other organisms. In Vincent's angina, the polymorphonuclears may decrease to 50-60 per cent. These cases improve rapidly on arsenical treatment internally and locally.

Surgical treatment.

It is our belief that in the majority of cases there is no obturating thrombosis of the large veins, but only phlebitis or mural thrombosis ; we may therefore expect recovery in the majority of cases when the primary focus of infection is eradicated, and when surgical metastases are properly met, without any surgical treatment of the internal jugular veins or other venous sinuses. When the first signs of thrombosis of venous sinuses appear, the condition must be met promptly surgically. We believe that the German methods are too radical, as is perhaps reflected in the high mortality which is reported from that country. We are in perfect accord with them, however, in the belief that early incision of external swellings even when there is no fluctuation to be found is necessary. The results in such cases are excellent, even though no pus may be found at time of operation. The greater and the earlier the external swelling appears, and the earlier it is met surgically (before it breaks through into a vein), the more hopeful is the prognosis. Hippocrates recognized this many years ago ; it is true to-day.

Weiss and Haenschell have reported prompted recoveries in post-anginal sepsis after removal of tonsils in acute stage ; this undoubtedly proves that in a small number of cases the portal of entry and focus of infection are identical. Uffenorde attacks the focus of infection from the outside; he lays open the jugular sheath and exposes the para-pharyngeal and retro-pharyngeal spaces ; the internal jugular is ligated ; then enucleation of tonsils is carried out. Zange, attacks the tonsils first and ties off the internal jugular ; then he cleans out all lymphatic glands in neck. Claus, ligates the jugular ; traces the facial veins to the tonsils and ties them off ; then enucleates tonsils. Clairmont has suggested an operation which in Germany is called ' Kollare Mediastinomie ' ; this consists of cutting off the lymphatic and venous channels which drain into the mediastinum. In œdema of larynx secondary to cervical abscess in these cases, Leider, without tracheotomy, obtained good results by opening lymphatic channels in neck (on the jugular) after extirpating the swollen lymphatic gland.

We have records of eight cases of sepsis following oro-naso-pharyngeal infection ; three of these patients died ; four completely recovered ; one left the hospital still running a temperature. In one case a definite sinus thrombosis (involving all venous sinuses) was demonstrated at autopsy, and the following metastatic lesions were noted, pneumonia, mastoiditis, cervical abscess, parotitis, endocarditis, peritonitis. In the two other cases which died no autopsies were performed.

The German belief that in all these cases there is a thrombosis of the internal jugular or of its large anastomosing branches is not borne out by our experience ; we believe that in all these cases there is thrombosis of small venules which acts as a focus of sepsis, but that these thromboses do not necessarily extend to the larger veins. In the majority of cases the thrombosis does not extend beyond the small veins. We feel that the suggestion that in post-anginal sepsis the internal jugular should always be tied is too radical

a measure. We believe that the local condition and infection should be eradicated first ; if the symptoms persist, then it would seem that ligation of internal jugular should be carried out. In a number of cases the mere enucleation of the tonsils in the course of sepsis, caused a subsidence of temperature and complete recovery.

It is of primary importance to incise and lay free all exudative swellings in the neck, and clean out all infected glands, in the presence of a post-anginal sepsis, even if there be no definite fluctuation to be ascertained.

The cases in which a cord-like swelling is felt in the neck along the margin of the sterno-cleido-mastoid muscle, or in any case which presents evidence of venous sinus or meningeal involvement, the ligation of the internal jugular should be carried out at once.

THE SURGICAL ANATOMY OF RAMMSTEDT'S OPERATION

BY

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It is generally admitted that Rammstedt's operation is not one of the easier ones of surgery, quite apart from the smallness and weakness of the patient. The main reason for its difficulty is that, while there is no margin whatever between the disaster of doing too little and the danger of doing too much, there are no clear indications to show that the object of the operation has been accomplished. In the published accounts there is a lack of definite landmarks to guide the inexperienced in the division of the muscle, and certain curious points about the relations of the different structures have never, as far as I know, been described. I have found the recognition of two of these, the narrowing of the bore of the mucosa at the pyloric orifice, and the zone of adhesion that follows it, of very considerable help in the operation.

The structures encountered in the freeing of the pylorus fall into five main groups. I propose first to describe them shortly, and then to show how their relations affect the operation and the various mischances that may occur in the course of it.

1. The serous coat.—This has no particular features to distinguish it from the visceral peritoneum covering the alimentary tract elsewhere. Two of its qualities which are of importance in the operation are that it is extremely adherent to the muscle beneath, and that it is tough and inextensible.

2. The blood vessels.—These run from two sources, the right gastric and gastro-epiploic vessels, and in two planes, a superficial and a deep. The superficial ones show conspicuously on the surface just under the serosa, but in the region of the operation they fail to make any visible anastomosis at the mid-point from their origins, as they do elsewhere on the stomach. The hiatus between them forms the well-known ' bloodless line ' which follows the axis of the viscus, and so is curved upwards at its left extremity.

The deeper vessels mostly ramify in the mucosa, but there are two which are almost invariably seen in the muscle during the operation. The most important of these is an artery, with its accompanying vein, which is met running across the duodenal end of the incision, just at the apex of the fornix of the mucosa, to which it forms a very useful indication. The other vessel appears in the deeper layers of muscle towards the other end of the wound, and occasionally causes trouble from bleeding.

3. The muscular coat.—The only known pathological change in the disease is an over-growth of muscular fibres, especially at the pylorus, and this results in a blockage there that is mechanical rather than functional[1].

This swelling of the muscle takes place inside an adherent and unstretchable covering of peritoneum, and consequently can go in two directions only,

inwards into the lumen, and lengthways, mainly into the duodenum. The result of the swelling inwards is that the pylorus, instead of being when relaxed the normal limp and patent tube, remains at all times a hard and solid mass with the muscle tightly filling the serous coat, as a cork does the neck of a bottle. The swelling downwards produces a protrusion of the pyloric orifice into the duodenum which is usually compared to that of the os uteri into the vagina, with, of course, a similar fornix of mucous membrane surrounding it.

Another mechanical effect of the confinement and hypertrophy of the muscle is a decrease in its vascularity, from the compression of the vessels supplying its fibres. At operation it is noticeable that there is much less oozing from the cut surfaces of the hypertrophied sphincter than there is from the normal fibres that may be cut at either end of it, or than there is if a normal pylorus be incised.

Finally the muscle is changed in consistency from its usual fibrous state to a crispness resembling that of young celery. As with celery, toughness ensues with age, and in the later stages of the disease the muscle is noticeably more fibrous and vascular than in the early ones. Presumably this is due to the beginning of that return to normal which will become complete if the child survives.

4. The areolar or submucous coat.—This inconspicuous layer makes the operation possible, and to understand its relations it is necessary to study its functions. Here as elsewhere in the body the areolar tissue exists to form a connection that will allow two structures to move freely on one another, and, as usual, one of these structures is muscle. The other is the mucosa, and the need for independent movement arises because it, being non-contractile, must meet the contractions of the surrounding muscle by wrinkling into folds inside it.

As might be expected, the amount and looseness of the areolar tissue and the depths of the folds are greatest at the points where the variations in diameter of the tube are greatest, and least where they are least. Thus the areolar layer is well marked in the pyloric antrum, becomes still wider and looser up the pyloric canal, decreases markedly over the projection of the sphincter, ceases entirely at the apex of the fornix, and then reappears again in the duodenum.

5. The mucosa.—This is the most important of all the layers, and the most difficult both to understand and to describe. In the pyloric antrum it is of considerable thickness and is wrinkled into longitudinal folds, which increase in depth as the pyloric canal is reached, and so give the well-known star shape of the potential cavity that is seen here on transverse section. These deep folds run through the canal till the actual opening into the duodenum is reached, when they suddenly cease just as the bore of the muscular tube starts to widen. Consequently at the apex of the pyloric protrusion into the duodenum, although the actual diameter of the mucous tube is far greater than that in the pyloric canal, the potential diameter is far less. In other words, if the entire mucosa in this region be freed of muscle and dilated to its full extent, it will be found that at the pyloric orifice there is a very sudden

and well marked ' choke ' in its bore, like that at the muzzle of some shotgun barrels.

At the end of this zone of constriction, which only lasts for about an eighth of an inch, the mucous membrane suddenly expands into the full diameter of the duodenum, which is approximately twice that of the choke and the same as that of the potential diameter of the pyloric portion. It runs backwards smoothly applied to the protruding nozzle of muscle to form the fornix already mentioned, and then forward again as the lining of the duodenum.

On consideration it will be seen that the apex of this fornix is subject to a considerable force tending to tear it downwards into the duodenum whenever

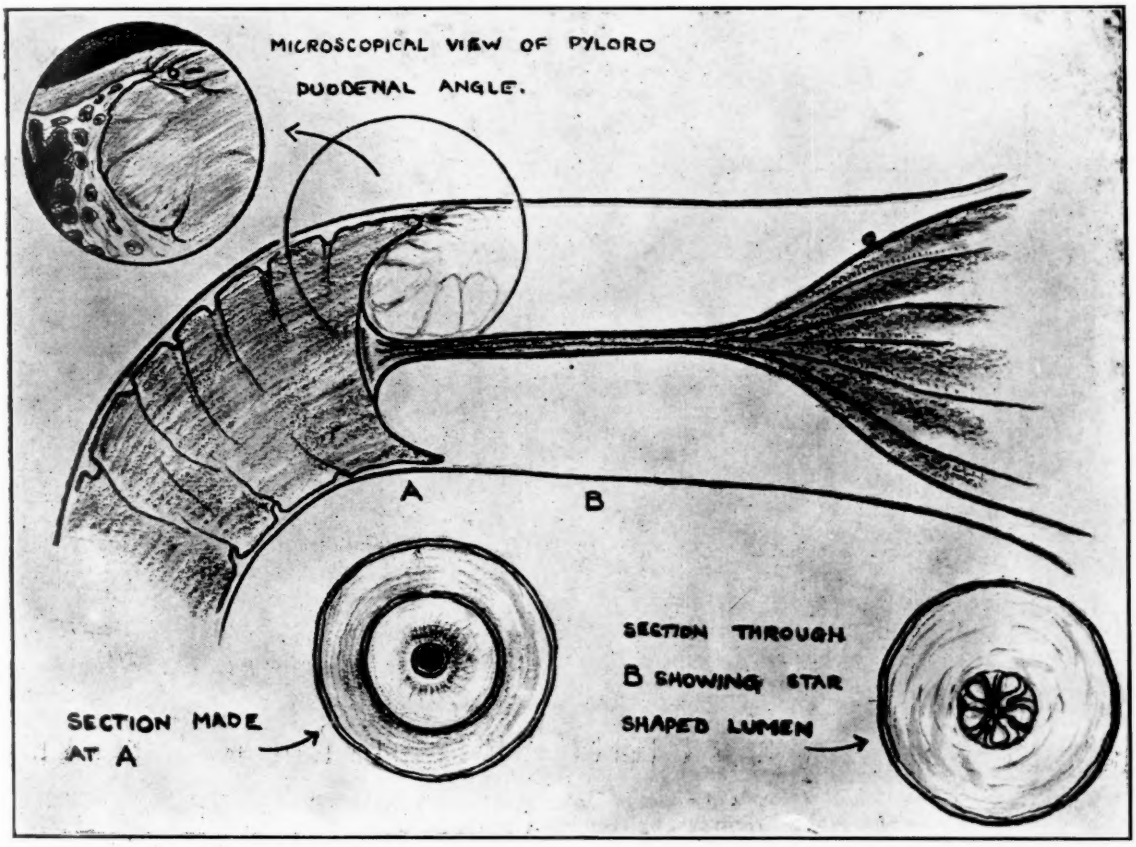

FIG. 1. Semi-diagrammatic sections of the hypertrophied pylorus. The microscopical view shows the fibrous bands radiating from the fornix of the mucosa, and the vessel running just outside it.

the stomach contracts against the stopper-like mass of muscle in the pylorus ; and as might be expected, this force is counteracted by a development of fibrous tissue, as in the similar case of the tonsil[2]. The fibres run, just as Lane's doctrine of the organization of lines of force would lead one to expect, outwards and backwards from the angle of reflection of the mucosa, into the muscle. In consequence a ' zone of adhesion ' is formed at this point, in which mucosa, muscle, and serosa are bound into one almost inseparable mass, but immediately beyond it the mucosa once again becomes rugose and lies loosely attached to the duodenal muscle (Fig. 1). In this area the mucous membrane

is a very vascular and vital structure, which can be stripped of all protection over a large area without any risk of sloughing. It is also, like all sheets of tissue, of surprising tensile strength as long as it remains uninjured, but once it has been punctured the tear will extend with the greatest readiness.

A final point for consideration is that the folds in the pyloric antrum may possibly form valves over the opening of the canal if this is allowed to remain very small. Whether this ever occurs in life I am not prepared to say, but it is certainly possible after death to produce a valve of this sort at the other end of some stomachs. In these water may be run in through a tube

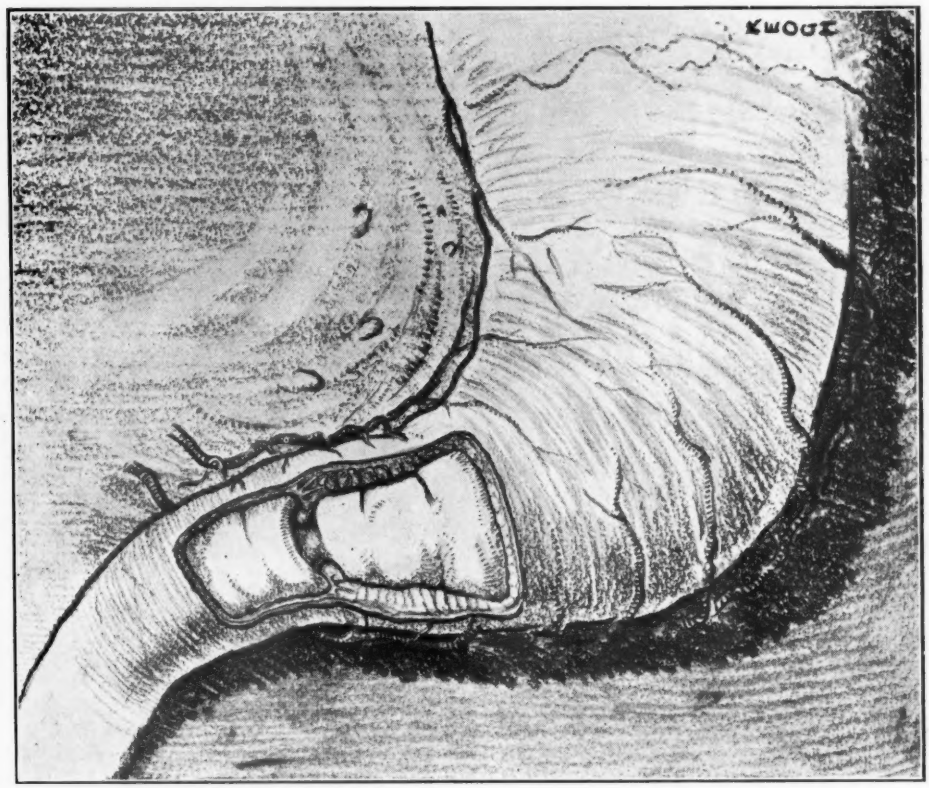

FIG. 2. Dissection of stomach of a case of hypertrophic stenosis with the muscle removed from an area of duodenum and pylorus, showing zone of constriction of mucosa.

in the cardiac orifice till it is under considerable pressure, but on withdrawing the tube folds of mucous membrane fall together to produce a valve and prevent its escape.

To confirm these observations it is necessary to make a rather difficult dissection. The first step in it is to fill the stomach with water to a fairly high tension by means of a tube passed into the cardiac orifice, after the duodenum has been closed by a ligature. Then an oblong area, as shown in Fig. 2, is marked out by an incision through the serous and muscular coats, and these are peeled off the mucosa from either end in towards the junction of the pylorus and duodenum. It will be found moderately easy to do this

till the adherent zone is reached; but here, as the tensile strength of the mucosa is less than that of its adhesion to the muscle, a separation can only be made by clean cutting. The best way at this point is to leave this patch of muscle adherent till the preparation has been hardened and fixed in its expanded state. It can then easily be cut away, and the result is as shown in Fig. 2, with the bulging mucosa clearly showing the zone of constriction.

Discussion.

The practical application of these points is fairly obvious. The right end of the incision is determined by the always clearly visible junction of the

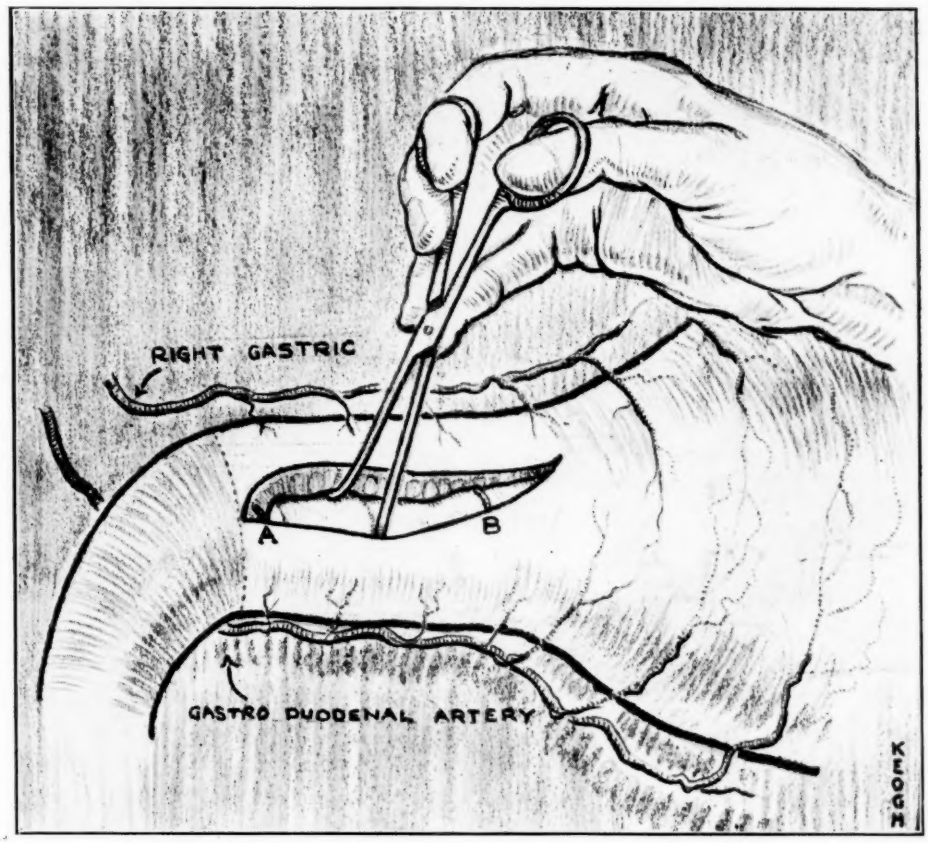

FIG. 3. Semi-diagrammatic drawing of Rammstedt's operation showing the vessels at either end of the incision, and the narrowing of the bore of the released mucosa at the zone of constriction.

whitish, opaque, and solid pylorus with the bluish, translucent, and flaccid duodenum. The cut should begin a millimetre or two short of this, and extend well into the pyloric antrum, curving upwards in its left third to follow the bloodless line between the superficial blood vessels. Most illustrations give the impression of too short an incision, and as there is no definite anatomical limitation in this direction, there is no reason for risking possible blockage here by curtailing the cut.

The mucosa is then exposed by blunt dissection, but exposure is far from being enough. The aim of the operation is not so much to allow the passage of food through the original pyloric canal, as to form a totally new one alongside it, by the bulging out of the uncovered mucosa. To do this at least half an inch of it should be exposed in the middle of the incision and as near as possible to either end. By far the easiest and safest way to do this is by stretching the edges of the incision in the muscle apart, so that they tear away from the intact mucosa beneath. Owing to the looseness of the subjacent areolar tissue this is perfectly safe and easy to do over the pylorus and on to the stomach, but it is a different matter at the duodenal end. Here the zone of adhesion is the danger, as although the muscle will split from the mucosa as easily in the duodenum as in the stomach, there lies between these two regions this ring in which serosa, muscle, and mucosa are all bound together, and will split together or not at all. If it were not for this it would be possible to divulse the muscle just as boldly at this end of the wound as at the other, and to leave the mucosa to take care of itself.

FIG. 4.

In avoiding this dangerous region there are two aids. The first is to remember that it is marked by the vessel described, and lies superficially, so that while it is risky to extend the wound near the surface, it is comparatively safe to stretch the deep muscle fibres till they part. The second aid is the recognition of the annular constriction, which is announced by the mucous membrance suddenly ceasing to bulge when it is released, and dipping down in the choke described. Thus the sign that the obstruction has been overcome is the paradoxical one that the calibre of the released mucosa suddenly narrows.

For the purpose of stretching the sides of the muscular incision apart no instrument in the surgeon's usual kit is really suitable, and I think it so important to have a complete control of this manœuvre that I have got Messrs. Weiss to make me a small stretcher with carefully blunted ends set at the correct angle to bite in the tough walls (Fig. 4).

If the surgeon is in any doubt about the freeing of a passage, he can test the duodenal end of it by invaginating the wall of the duodenum with a blunt pointed pair of artery forceps, and pushing them through the pyloric opening till they can be felt under the freed mucosa. This is usually quite easy to do, but in some cases the pylorus cannot be delivered far enough to allow it.

Mischances of the operation.—The first of these is the opening of the abdomen on a wrong diagnosis, because of spasm of the pylorus instead of true hypertrophic blockage. I have done this twice, and on each occasion cured the vomiting by performing Rammstedt's operation on the normal pylorus, throwing it out of action just as the sphincter ani is put at rest by division in treating a fissure. I had learnt by post-mortem experiment that it is easy enough to divide the normal pyloric muscle, and though no one would deliberately operate for pylorospasm I see no contra-indication to cutting the sphincter once the pylorus is exposed.

The second mischance is the puncturing of the mucosa, and though this is alarming enough, it is less serious than might be expected. I know of at least six cases in which it has happened, but none of them resulted fatally. The reason for this may be that the point at which it invariably occurs, the end of the fornix of the mucosa, on the upper side, is almost entirely immune from the pressure, or even the contact, of fluid passing down the duodenum.

The third and most serious of the mischances is the failure to relieve the blockage of the pylorus, and when this occurs the only chance lies in a second operation to complete what should have been done at the first. I have had one case of this sort, and though the child ultimately recovered, it was that contretemps which stimulated me to the studies resulting in this paper.

I have to thank Dr. C. A. Keogh for his excellent drawings, and also for suggesting the real function of the zone of adhesion.

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PINK DISEASE : ITS MORBID ANATOMY, WITH A NOTE ON TREATMENT

BY

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In its clinical aspect, pink disease has received a great amount of attention, as can be seen from the abundant case reports in the literature. Its pathological investigation, however, has been served less well, for, although most of the symptoms point to a nervous disorder, very few autopsies have included a microscopic examination of the nervous system. The main object, therefore, of this paper is to record the results of the histological examination of the nervous system in seven cases of pink disease.

The pathogenesis of the disease remains unrecognized, but various views as to its causation will be touched upon. Lastly, we offer a few notes on the results of a certain form of treatment which appears to be of definite value.

Historical.—It is difficult to say if we are dealing with a new disease. Certainly in the literature no mention of the condition can be found earlier than 1903, but various authorities have remarked that they were aware of its clinical features prior to that date.

The first mention of the disease appears to have been made in 1903 by Selter[1], who described eight cases at a medical society meeting for children's diseases at Cassel (Germany). Since then one or two of his cases have been regarded as doubtful. The title employed by Selter for the condition was 'trophodermatoneurose' or 'vegetative neurosis.' This early communication, however, escaped attention, and a wider interest was not aroused until several years later when many cases were described in Australia.

In Australia, Swift[2] of Adelaide in 1914 reported 14 cases under the title of 'erythredema.' Between 1917 and 1920, Wood and Cole[3] of Melbourne collected 91 cases, and Wood remarked that he had 'frequently seen . . . cases in Melbourne for the past thirty years.' In Sydney, Clubbe, Littlejohn[4] (1923), and others had for many years been familiar with the condition, and were in the habit of referring to it as 'the pink disease.'

In America, Byfield[5] (1917 and 1920), and Bilderback[6] (1919), recorded numerous cases, which were soon followed by the reports of many other observers. The earliest examples to be described in Great Britain were by Parkes Weber[7] in 1921, and Thursfield and Paterson[8] in 1922 (dermato-polyneuritis). In Germany for the second time the syndrome was described, on this occasion by Feer[9] in 1923. In France, Haushalter[10] (1925), wrote on a 'neuro-vegetative syndrome' in infants, and mentioned that he had been aware of the condition since 1911. The disease has also been recorded in several other European countries.

For the sake of simplicity the commonplace name of 'pink disease' will be employed in this paper, though the terms 'trophodermatoneurose' of Selter, and 'neurosis of the vegetative nervous system' of Feer, are of value

in indicating that the symptoms are mainly related to the vegetative nervous system. Erythrœdema is an unfortunate title, as there is no true œdema of the parts affected.

Symptomatology.—The syndrome known as pink disease wears such a distinctive stamp that the diagnosis is usually apparent at a glance. Conspicuous symptoms are irritability, photophobia, bluish-red discolouration with slight swelling of the hands and feet—' raw-beef hands and feet '—excessive sweating, muscular hypotonicity, and in some chronic cases sensory impairment and loss of the tendon jerks.

The disease is one of infancy and early childhood, affecting both sexes equally, most cases occurring between the ninth and eighteenth months. Infants as young as four months are not infrequently affected, and more rarely, children up to the seventh year. The youngest case we have personally observed was a breast-fed infant of ten weeks, in whom the symptoms commenced in the third week after birth. It occurs in the breast-fed as well as in the artificially-fed infant, and both in rural and urban areas. The time of year in which the greater number of cases are met with is between autumn and early spring. Most cases are sporadic, and there is no evidence that the condition is infectious. Nevertheless, a tendency to grouping of cases by locality suggestive of small epidemics has been noted by several observers (foyers epidemiques, inseln).

The sequence of events in a typical case is as follows :—Soon after some respiratory or intestinal catarrh, or without prodromal symptoms of infection, the child becomes acutely miserable and irritable, sleep is disturbed, appetite reduced, photophobia appears, and the hands and feet become cyanosed, bluish-red, slightly swollen, glazed, and very cold. A pink erythematous patch is usually present on the point of the nose and both cheeks. Rashes of a papulo-macular type occur on the body, but most often on the extremities only, reaching as far up the limbs as the wrists and ankles. Sweating is a prominent symptom, and may be extreme, and is frequently the cause of a miliary sudaminal rash covering the body. The pulse rate is accelerated, commonly to between 120 and 160 beats per minute, and in many cases the blood pressure is raised (110 to 130 mm.). Despite the sweating and quickened pulse the temperature is always normal in an uncomplicated case.

A characteristic position in bed is often assumed, the knee-elbow position, in which the child rubs and burrows its face in the pillow, at the same time keeping the light from its eyes. Apparently there is a great deal of painful irritation of the extremities which may be likened to the paræsthesiæ experienced by the adult patient affected with acroparæsthesia or with erythromelalgia. The intolerable itching and prickling cause the infant or young child to bite the fingers and rub the legs together, which habit in conjunction with the sodden state of the skin often leads to the appearance of ulcers and septic blisters on the fingers and feet. At an early stage of the disease the surface epidermis of the hands and feet begins to desquamate in fine flakes. A fairly profuse nasal discharge, often of clear mucus, and a tendency to increased salivation are noticed in many cases.

As the disease progresses the limbs become markedly hypotonic, and in chronic cases after three months or so the knee and ankle jerks are often lost, and sensory changes, of which analgesia is the most easily tested, may be observed.

In the more severe cases remarkable trophic disturbances are likely to occur. Several teeth may become loosened and even fall out. This has also been recorded as one of the earliest symptoms (Rocaz[11]). The gums may become detached from the alveolus. For example, in the case of an infant of eighteen months, seen by one of us, there were signs of a general improvement at about the end of the third month of illness, when to the mother's surprise one day she found that on pulling down the lower lip the whole of the gum came away from the lower jaw revealing the teeth down to their roots. The child was afebrile, but died in hyperpyrexia later in the same day. The nails have become loosened and shed in some cases. More often septic sores or ulcers form at their bases or on the palmar surfaces of the fingers and feet. Gangrene of the finger-tips has also been recorded (Parkes Weber[7], Debré and Petot[12]).

The disease runs a chronic course, often with periods of partial remission, and lasts commonly for several months to over a year. Abortive cases, however, are also recognized. As recovery takes place the capillary stasis at the extremities becomes intermittent, so that the cyanosis comes and goes, sometimes being present in one hand for a while and not in the other, and vice versa. The mortality is roughly about 5 per cent. (Muller[13]), most of the deaths being due to some intercurrent infection such as broncho-pneumonia, but occasionally the disease per se proves fatal, sometimes by cardiac failure (see Cases 4, 7).

From a clinical survey of pink disease, it is apparent that nearly all the symptoms are due to a disturbance of the vegetative nervous system (sympathetic and vagus). This important fact has been specially emphasized by Feer, who drew attention to the rise of blood pressure and of pulse rate during the disease without any corresponding rise of temperature or respiratory disturbance. The outstanding symptoms of 'vegetative' disturbance are vasomotor paralysis at the extremities, acceleration of the pulse, raised blood pressure, excessive sweating, and trophic changes. To a similar cause, in all probability, are due the photophobia without conjunctivitis, the rhinorrhœa, the sialorrhœa, and the anorexia. At a later stage of the disease evidence of lower (spinal) neuron implication is often discernible in the abolition of the tendon jerks and the presence of analgesia. In an uncomplicated case other systems than the nervous are unaffected.

Clinical pathology.—The state of the cerebrospinal fluid is normal. Blood cultures have been negative and those from the nasopharynx yield the common types of bacteria. In the blood a leucocytosis is a constant finding, granular cells predominating. The Wassermann reaction is negative. A secondary infection of the urine with bacillus coli is not uncommon. Analysis of the stomach contents revealed 'a practically normal amount of hydrochloric acid' (Byfield[5], 1920).

Clinical and pathological reports.

Our investigations on the pathology of pink disease are based on the following seven fatal cases.

Case 1.—J. N., a female child, aged 2 years and 7 months, was admitted to hospital, August 21st, 1923.

For five months previously the child had been ailing with pains in the abdomen, unaccompanied by vomiting or diarrhœa, and with pains in the limbs. In the last two months the extremities had been noticed to be very cold and reddened, and for about six weeks there had been considerable weakness of both legs.

On admission the child lay flat in bed unable to sit up, and sweating was profuse. Photophobia, insomnia, anorexia, and increased thirst were observed. There was a striking coldness of the limbs, especially of the hands and feet, which were bluish-red and desquamating. A

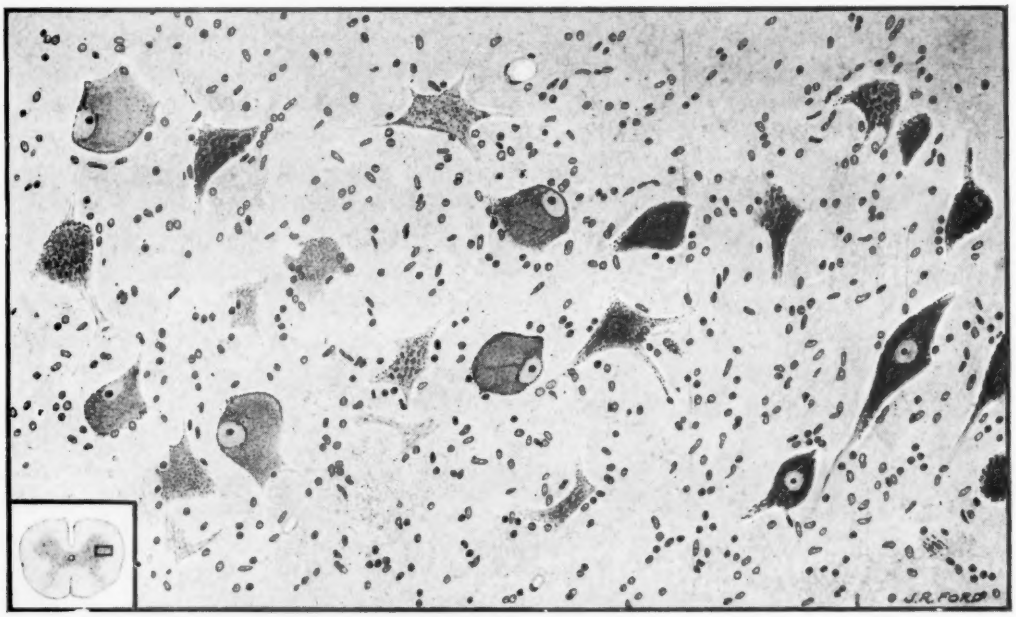

FIG. 1.—Drawing of an anterior horn of the spinal cord at the level of the fourth lumbar segment from Case 1. Stained by toluidin-blue (Nissl method). × 200. Many anterior horn cells show advanced chromatolysis.

sudaminal rash covered the trunk. Small abrasions were present on several of the toes. There was a complete flaccid paralysis of both legs, but movements of the arms were fairly good. All the muscles were extremely hypotonic, and no tendon jerks could be obtained. Cutaneous sensibility was impaired over the entire body (analgesia).

The pulse rate varied between 110 and 160; the temperature was normal. Blood count: leucocytes 23,600, 77·5 per cent. being polymorphonuclear cells. Cerebrospinal fluid was normal. Cultures:—C.S.F., negative; fæces, usual bacteria; urine, a few B. coli.

The child had one short remission with improvement, but afterwards went downhill. The muscles of the upper arms became weak, and towards the end there was a slight right facial paralysis. Swallowing was never disturbed. Death occurred from broncho-pneumonia on November 21st, 1923, after an illness lasting roughly eight months.

AUTOPSY.—The body was that of an emaciated child. There were some swelling and cyanosis of the fingers, and an ulcer on the outer border of the left thumb penetrating down to the periosteum.

The surface of the brain showed a little congestion; the spinal cord was pale and firm to touch. Numerous portions of the brain, spinal cord, peripheral nerves and vagus were taken for section. Both lower lobes of the lungs were consolidated, and the pleural cavities contained a small quantity of free fluid. Other organs, heart, liver, spleen and kidneys, appeared congested, but were otherwise normal. There was no enlargement of the lymph glands.

MICROSCOPICAL EXAMINATION.—Sections from the thoracic and abdominal viscera appeared normal, except those from the lower lobes of the lungs which showed signs of broncho-pneumonia.

In the nervous system sections* from the cortex, pons, medulla, and cerebellum were normal. In the spinal cord at the level of the seventh cervical segment several anterior horn cells showed a slight degree of chromatolysis. In addition, there was satellitosis of some cells. In the lumbar enlargement, particularly in the fourth and fifth lumbar segments, advanced chromatolytic changes were observed in the anterior horn cells. Most of these cells were rounded and their nuclei were either grossly eccentric, lying just under the cell membrane, or had disappeared. Fig. 1 represents the condition of the anterior horn cells in the fourth lumbar segment. Satellitosis of the chromatolytic cells may be noted.

Throughout the length of the cord a slight diffuse infiltration with small round cells was present. In the lumbar region this infiltration was particularly noticeable in the anterior horns. There was no obvious increase in the number of small cells in the anterior or posterior roots.

The capillaries in the spinal cord were congested, especially those in the nerve roots of the lumbo-sacral segments.

Many nerves were stained by the Marchi-Busch method with negative results. The same nerves stained by the Weigert-Pal method exhibited varying degrees of myelin degeneration.

In the sciatic nerve some fibres were well stained. Others were poorly stained and were swollen, often showing much beading and fragmentation of the myelin. Many fibres had globular formations of degeneration products along their course. There were an undue number of non-myelinated fibres present in this nerve. This was particularly well seen in cross section. The internal saphenous nerve showed somewhat patchy staining of the myelinated fibres, but they appeared well myelinated. In the brachial plexus there were many thinly myelinated fibres. There was much fragmentation of the myelin in some fibres, and in others the myelin sheath was swollen and broken up. In the median nerve many fibres showed swelling of the myelin sheath, but most fibres were well myelinated. The fibres of the vagus nerve appeared healthy. The Gasserian ganglion presented no abnormalities.

The muscles of this case were compared with similar muscles from a child of the same age who died after a surgical operation. The fibres of the biceps brachialis in the control were of uniform size and showed distinct cross striation. The same muscle of J. N. had smaller fibres and cross striation was not so obvious. On cross section many fibres were rounded and in certain portions of the muscle there was an apparent increase in the number of sarcolemmal nuclei. In the biceps femoris the proportion of small fibres was greater than in the biceps brachialis, and cross striation was very poor. The fibres of the diaphragm appeared normal in size and cross striation was good. By the Weigert-Pal method the intramuscular nerve bundles in the muscles of the control case were stained a deep black. In the biceps brachialis and biceps femoris of J. N., the nerve bundles stained poorly. Some of the smaller nerve bundles showed practically no myelination. In the larger nerve bundles, the myelinated nerve fibres appeared to have swollen myelin sheaths. In the diaphragm, the nerve bundles were well myelinated.

Case 2.—P. E., a female child, aged 7 months, was admitted to hospital, October 17th, 1924.

The infant was breast-fed. At five months she began to sleep badly, lost interest, and cried much. A morbilliform rash appeared, covering the body, and was very irritating. Later the palms began to peel. Sweating was profuse. The bowels were regular, and respiratory catarrh absent.

On admission, the child was well nourished, but had a profuse pin-point papular rash over

*The nervous system in our seven cases was stained by various methods. All were stained by the Nissl method, hæmotoxylin and Van Gieson, Scharlach R. method for fat, and the Marchi-Busch method for recent myelin degeneration. Certain of the more chronic cases were also stained by the Weigert-Pal method, and by Anderson's Victoria blue stain for neuroglia.

the body, and the hands and feet were cold and raw-beef colour. There were erythematous patches on the nose and cheeks. No evidence of glandular enlargement was present.

The child had some difficulty in holding up the head, and the muscles of the arms and legs were hypotonic and feeble. The knee and ankle jerks were present, and sensation was unimpaired. The pulse rate varied between 120 and 150; the temperature was normal until pneumonia supervened as a terminal event. Death occurred October 24th, 1924, after an illness of roughly two months.

AUTOPSY.—The body was that of a fairly well nourished infant. Peeling of the skin of the hands and feet was observed, and there were several small ulcers on the fingers of the right hand. The hair could be pulled out in handfuls.

The macroscopic appearance of the brain and spinal cord was normal, and the other organs showed no abnormality beyond some basal congestion of both lungs.

MICROSCOPICAL EXAMINATION.—Early broncho-pneumonic changes were seen in sections of the lung. Sections from the liver, spleen, kidneys, thyroid and thymus appeared normal.

The only abnormalities presented by the cerebral cortex and the brain stem were an increased vascularity of the capillaries and a slight infiltration of both the white and the grey matter with small round cells. The medulla showed a similar infiltration with small cells, but no engorgement of vessels. The cellular infiltration appeared to consist of the same type of cell as we observed in the spinal cords of this and our other cases.

In the spinal cord, one or two rounded anterior horn cells were seen at the level of the fifth lumbar segment. Otherwise the cells of the spinal cord seemed healthy. In the cervical and lumbar enlargements a diffuse infiltration of the cord with small cells was evident.

In sections of the cord stained by the Marchi-Busch method, fine black droplets representing degenerating myelin were seen in the dorsal roots and running into the posterior horns in the cervical enlargement. A similar appearance presented itself in the lumbar enlargement, where black droplets were seen in both the anterior and posterior roots, though more evident in the posterior roots. The dorsal region of the cord did not show any abnormal staining by this method.

The sciatic, anterior tibial, posterior tibial and vagus nerves were examined by the Weigert-Pal and Marchi-Busch methods, both of which gave negative results. The sensory nerves in the skin of the foot were easily discernible by the Weigert-Pal method, as they were heavily myelinated. The intramuscular nerve bundles in the biceps femoris, gastrocnemius and diaphragm were also well myelinated.

Whereas the size and shape of the muscle fibres were normal in the biceps and diaphragm, in the gastrocnemius many of the fibres were definitely smaller than in a control muscle and cross striation was not so obvious. The sarcolemmal nuclei were increased in number, especially in relation to the thin fibres.

Case 3.—M. B., a female child, aged 1 year and 11 months, was admitted to hospital, January 16th, 1925.

Six months before admission a rash appeared on the arms and legs and to a less extent on the trunk. The mouth was sore and some diarrhœa was present with a slight rise of temperature. A month later the hands and feet became swollen and reddened, and the infant was very miserable, continually rubbing the legs together. She was able to stand with support, but was weak and listless.

On admission the child was fairly well nourished, but was restless and fretful. The hands and feet were pink, swollen, and cold, and there were erythematous patches on the nose and cheeks. Fine desquamation was occurring on the cheeks, feet and hands. Photophobia was present.

The muscles of the upper and lower limbs were weak and very flabby. No tendon jerks were obtainable. There was some anæsthesia of the hands and of the legs as far up as the knees.

The inside of the mouth became ulcerated, and numerous boils kept forming on the body. The stools were loose and contained much mucus and undigested food. The temperature was raised to 100°. Death occurred 14 days after admission, and was due probably to toxæmia The duration of the illness was roughly six months.

AUTOPSY.—The body was that of a poorly nourished child, with numerous pustules on the trunk and limbs.

MICROSCOPICAL EXAMINATION.—No abnormality was detected in sections of the liver, spleen. kidney, or heart muscle.

In sections of the cerebral cortex and basal ganglia, stained by hæmatoxylin and Van Gieson, a large number of small round cells were seen scattered throughout the white and gray matter. These cells were not the nuclei of fibroglia as no processes could be stained by neuroglia methods. We took them to be the same type of cell as we have described in the spinal cords of our other cases and which we also found in the spinal cord of this case.

The cellular infiltration in the spinal cord was generalized. It was present throughout the length of the cord and in both the white and the gray matter, but it was most obvious at all levels in the dorsal horns.

The anterior horn cells were normal except in the lumbar enlargement, where one or two showed eccentricity of the nucleus with chromatolysis.

The sciatic, femoral, popliteal and musculo-spiral nerves were examined by the Weigert-Pal method and by the Marchi-Busch method. The former gave negative results, but by the Marchi-Busch method degeneration of myelin was observed in the popliteal nerve.

No muscle was examined in this case.

Case 4.—P. M., a female child, aged 9 months, was admitted to hospital on June 8th, 1925.

Three weeks before admission the child began to draw up the legs as if in pain, rubbing the feet and hands together, and sweating profusely. The baby was very fretful and getting thin, though taking food fairly well, and was flabby, being unable to sit unsupported. The diet had been Nestlé's milk up to the seventh month, subsequently cow's milk.

On admission the child was very restless and miserable, shunned the light, and was unable to sit up. There was a papular rash over the body, and the feet and hands were typically 'pink.' The tendon jerks were present, and no sensory impairment was made out.

The pulse was usually 120, and the temperature was normal. Death occurred suddenly two days after admission without any physical signs of pneumonia, but with a terminal temperature of 104°. The duration of the illness was about three months.

AUTOPSY.—The body was well nourished with the pink colouration of the fingers and toes still visible. No signs of pneumonia were present in the lungs. In the heart the right auricle and ventricle were dilated. The thymus was larger than normal for a nine months infant. The abdominal viscera appeared healthy. The brain and spinal cord showed no abnormality.

MICROSCOPICAL EXAMINATION.—Sections of the spleen, pituitary, thymus and suprarenals appeared normal.

No abnormality could be seen in sections from the cerebral cortex, or from the medulla.

In the spinal cord there was a slight excess of small cells in the white and gray matter, not confined to any special area of the cord, or more apparent at any particular level.

The anterior horn cells appeared healthy in all regions of the cord.

The sciatic, internal and external popliteal nerves were examined by the Weigert-Pal and Marchi-Busch methods with negative results. No evidence of degeneration could be observed by either method. The vagus was unfortunately not examined.

Case 5.—R. S., a male child, aged 7 months, was admitted to hospital on February 22nd, 1929.

Two weeks before admission a rash developed on the hands and arms, and in the past three days peeling had occurred. The child was a full-time baby, born of healthy parents and had been quite normal up to six weeks before admission, when teething began and weight was lost. Since then there was a history of an unusual amount of crying and that the child had been observed to sit or lie with his head buried in the bedclothes. The bowels had been regular and there had been no vomiting. The child had been fed on the Allenbury sequence, 1, 2, 3, with occasional orange juice.

On admission the patient was found to be irritable with a red papular eruption on the hands, arms, feet, cheeks and nose. There was some peeling of the nose and hands. The condition was typical of pink disease. Two teeth had erupted. The gums were swollen, but there was no stomatitis. A purulent conjunctivitis of the right eye was present, growing staphylococcus aureus on culture. The pulse rate was rapid. No definite signs could be found of involvement of the nervous system. The reflexes were brisk and there was no definite evidence of sensory

changes. The stools were healthy on admission, but subsequently became loose, green and frequent, causing the buttocks to become sore and excoriated. The temperature rose and the general condition rapidly became worse. The child died on March 4th, 1929, after an illness of about five weeks.

AUTOPSY.—Performed six hours after death. The body was that of a well-nourished child. There was peeling of the hands and feet. Signs of a rash on the arms and feet were still present in the form of small subcutaneous red spots.

The brain and spinal cord showed no macroscopic abnormality. Portions of the median, ulnar, sciatic, posterior tibial and vagus nerves were taken for section. The heart and pericardium appeared normal. The lower lobe of the left lung was very congested, but still crepitant and there was no definite evidence of consolidation. The stomach and duodenum were normal. The lower end of the ilium was very congested and showed a few ulcerated areas about the size of a pea which were denuded of epithelium and had raised edges. Similar areas were found scattered throughout the large bowel. The liver, spleen, kidneys, suprarenals and pancreas appeared normal.

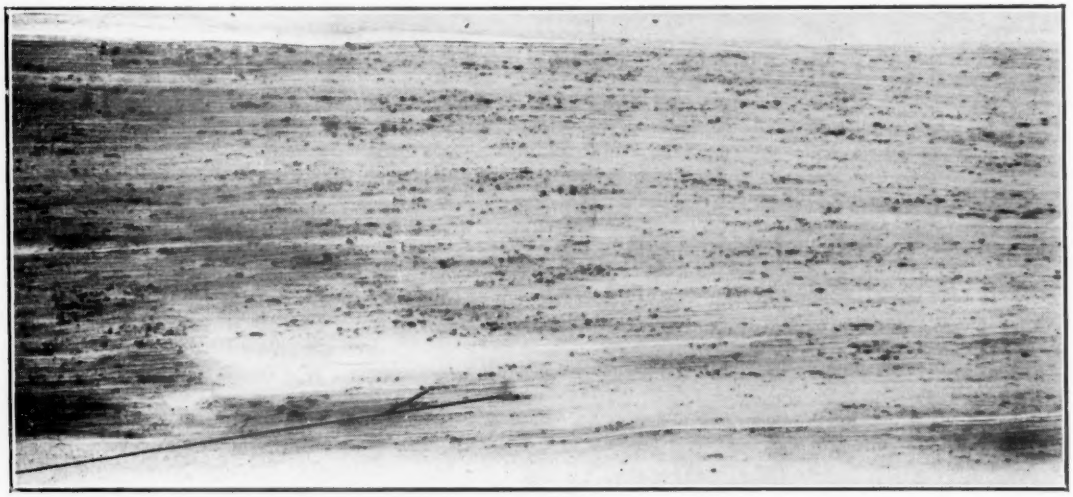

FIG. 2.—Microphotograph of a section through the median nerve of Case 5. Stained by the Marchi-Busch method. Black droplets of degenerating myelin can be seen scattered along the course of the nerve. × 120.

MICROSCOPICAL EXAMINATION.—Sections of all the viscera appeared normal, except those from the spleen. On section this organ was more congested than normal and had an abnormally large number of red blood corpuscles in the pulp.

The cerebral cortex, the brain stem and the medulla appeared normal by all staining methods.

The spinal cord, when stained with hæmatoxylin and Van Gieson's counter-stain, showed a diffuse infiltration with small round cells in both white and the gray matter. The infiltration was most apparent in the lumbar region, but did not seem to involve the posterior roots more than the anterior roots. The infiltrating cells were not fibroglial, i.e., they showed no processes when stained with neuroglial stains. They corresponded exactly in appearance to the small round cells infiltrating the spinal cord, described by Paterson and Greenfield in their cases. They were probably lymphocytes. The Marchi-Busch method did not reveal any degeneration of roots or tracts in the spinal cord.

The anterior horn cells of the spinal cord appeared normal when stained by the Nissl method except at two levels. In the region of the cervical enlargement several rounded cells that had lost their processes were seen, and at the level of the third to fourth lumbar segment there were

several pale cells, one cell of the antero-medial group having an eccentric nucleus and no Nissl granules.

The most striking changes denoting recent myelin degeneration in the peripheral nerves were obtained by the Marchi-Busch method. Degeneration of myelin was seen to some extent in all the peripheral nerves, but was much more evident in some nerves than in others. In the median nerve advanced degeneration was present in many fibres. No one fibre was completely degenerated throughout its length, but viewed in longitudinal section fat globules could be seen at varying distances along the course of almost every fibre (Fig. 2). In the ulnar nerve there were not so many fibres undergoing degeneration as in the median nerve, but early changes in the form of small black globules were easily recognizable. In the sciatic nerve very few fibres appeared degenerated. In the posterior tibial nerve many fibres in each nerve bundle were seen to be in a fairly advanced stage of degeneration. In the vagus nerve the great majority of the fibres appeared normal, but one or two showed early degeneration.

The nerves when stained with hæmatoxylin and Van Gieson's counterstain presented no abnormalities. There was no cellular infiltration and no thickening of the neural sheaths.

The fibres of a portion of the biceps femoris muscle were entirely normal in size and structure.

Case 6.—B.G., a female child, aged 7 months, was admitted to hospital on August 14th, 1929.

The history from the mother was that the child had lost weight from the age of 5 months, even while still breast-fed. She had been fed at the breast until the age of 5½ months and had then been given cow's milk with egg yolk and orange juice. There had been severe loss of appetite and the child had been sleeping badly. The bowels had been loose when the symptoms first appeared, but had since been constipated.

On admission the patient was seen to be a restless crying child. The back and front of the chest and the abdomen were covered with a fine erythematous rash which appeared to be irritating. On the chest also were one or two ulcerating septic spots. The hands were red and covered with the same rash; the skin of the hands seemed to be slightly puffy. The fingers were peeling. Just above the left ear was a hard inflamed swelling, about two inches in diameter, which was full of pus. This was aspirated and a perchloride dressing applied.

There was marked loss of tone in all the muscles, more particularly in those of the thigh and upper arm. The knee-jerks, however, were present. There was apparent impairment of sensation over the feet. The apex beat was rather diffuse, but strong, and was felt in the fifth and sixth spaces, inside the nipple line.

The child was very restless and spent most of her time with her face buried in the pillow. Two days later she was much quieter, but listless. Another septic boil appeared on the back of the head, and two others on the back. These were opened next day, but the child died the following day after an illness of roughly two months. The pulse rate at death was 160, temperature 103·6°.

Autopsy.—Performed 26 hours after death. The body was that of a poorly nourished child. The legs were œdematous. The thumb and inner two fingers of the right hand were desquamating and a vesicle was present on the big toe of the left foot. A rash was present on the buttocks, and sites of abscesses could be seen behind the left ear and at the back of the head.

The thymus extended downwards as far as the upper border of the heart. The right ventricle and auricle contained post-mortem blood clot. The heart was otherwise healthy. In the abdomen a large number of enlarged soft mesenteric glands were present. These glands were of normal consistency. The liver was fatty but not flabby. The spleen was firm and the Malpighian corpuscles stood out plainly. Both kidneys were pale and the left one showed fœtal lobulation. The stomach contained coffee-ground material and mucus. The œsophageal opening was injected and showed petechial hæmorrhages. Otherwise there was no evidence as to the origin of the blood found in the stomach.

The brain and spinal cord presented no macroscopic abnormality. Several peripheral nerves were removed for histological investigation.

Microscopical examination.—Sections of both lungs showed the typical early broncho-pneumonic changes of catarrh of the bronchi with polymorphonuclear exudate. Liver:—slight

fatty degeneration was present in the liver cells. Kidneys:—cloudy swelling was seen in the convoluted tubules. Sections of the spleen and intestine appeared normal.

In the skin, hyperkeratosis was the outstanding lesion. We did not observe any cellular infiltration. There were a very large number of sweat glands present in the portion of skin examined, probably an excess of the number normally present.

All parts of the nervous system above the level of the medulla appeared normal.

In the spinal cord the anterior horn cells were healthy at most levels, but at about the second or third lumbar segment a few cells of the anterior group had eccentric nuclei and were rounded and pale, with their Nissl granules clustered irregularly around the nucleus. A generalized infiltration with small round cells was found throughout the cord, but this infiltration was greatest in the lumbar region, where, in one or two sections, a special accumulation of cells was present at the entry zone of the posterior roots. The character of the infiltrating cells was the same as those observed in our other cases.

The sciatic, external popliteal, dorsalis pedis and musculo-spiral nerves all showed early degeneration of their fibres by the Marchi-Busch method. The degeneration was not wide spread

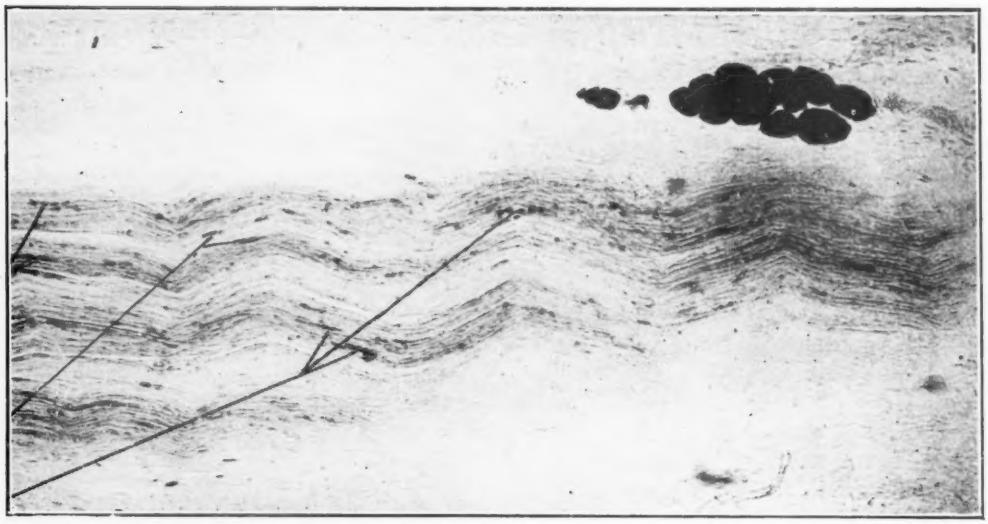

FIG. 3.—Microphotograph of a longitudinal section through the vagus nerve of Case 7. A number of black droplets representing degeneration of myelin may be seen. × 120.

in the nerves, but was confined to parts of the fibres, being always more advanced and more apparent at the nodes of Ranvier. No degeneration was seen in the phrenic nerve.

When stained by hæmatoxylin and Van Gieson, none of the nerves exhibited any cellular infiltration, but there was a slight proliferation of the nuclei of the sheath of Schwann.

No muscle was examined in this case.

Case 7.—D. B., a male child, aged 1 year and 3 months, was admitted to hospital on May 23rd, 1930.

The history obtained was that the child had been perfectly healthy up to one month before admission when he seemed to lose strength, ceased to walk and to talk, refused his food, became very irritable, and developed a sore mouth. He had been breast-fed for three months, was then given Savory and Moore's food until nine months of age and since had been on a mixed diet.

On admission the patient was found to be a miserable child with flabby muscles. There was marked stomatitis and the teeth, though healthy, were all loose. The skin of the hands and feet was pink and the condition typical of pink disease. The knee-jerks were present. The pulse rate, already high, rose to 164 per minute the day after admission, when the child collapsed and died suddenly. The length of the illness was roughly one month.

AUTOPSY.—Performed 48 hours after death. Traces of a pink eruption were still present on the hands and feet. No macroscopic abnormality was seen in the brain or spinal cord. Portions of many nerves were taken for section. The lower lobes of both lungs were congested. The heart muscle was contracted: death had occurred in systole. There was no dilatation of the right side of the heart. The muscle was not abnormally pale or easily friable. The stomach was large and atonic. There were slight inflammatory changes in the stomach wall. The intestines appeared normal. The liver showed a moderate degree of mottling due to fatty change. The spleen, kidneys and suprarenals appeared healthy.

MICROSCOPICAL EXAMINATION.—Sections of the heart muscle, thymus, lung and spleen appeared normal. In sections of the liver cloudy swelling and early degeneration of the tubular epithelium were seen. There was a slight degree of fatty change in the liver cells.

The cerebral cortex, mid-brain, pons and medulla appeared normal.

The whole length of the spinal cord was not available for section, but portions were taken from the lower cervical, mid-thoracic and mid-lumbar regions. The anterior horn cells in sections made at these levels showed no evidence of chromatolysis or other abnormality. There was a slight excess of small cells in both the white and gray matter of the portions of the spinal cord which we examined, but this cellular infiltration was less than in our other cases.

The sciatic, posterior tibial and cervical sympathetic nerves did not present any evidence of degeneration when stained by Scharlach R. and by the Marchi method. In the vagus nerve, a number of fibres showed definite degenerative changes by both these methods. With the Scharlach R. stain we observed swelling of the nerve fibres and fragmentation of the myelin. The picture exhibited by the Marchi-Busch method is represented in Fig. 3. It will be seen that no one fibre has degenerated throughout its course, but that many fibres have begun to degenerate in part of their course.

No muscle was examined in this case.

Pathology.

The immediate cause of death in pink disease is usually an intercurrent infection, such as broncho-pneumonia, or a concomitant disease, such as tuberculosis. In Wood's series of 91 cases there were five deaths, of which four were due to broncho-pneumonia. The pathological picture, therefore, of pink disease is apt to be complicated by the morbid histology of a secondary disease process. It is for this reason that the pathological examination of the nervous system is of great importance, as the changes which have been reported in the nervous system in certain cases of pink disease cannot be ascribed to the terminal complications of the disease. They depend upon the disease itself.

The pathological findings which Wood reported in three of his cases were essentially those of broncho-pneumonia. The nervous system was not examined pathologically. No autopsy was performed on the fifth patient, who died suddenly of heart failure. Byfield was one of the first to examine the nervous system. His case was a relatively acute one complicated by tuberculosis, which produced characteristic lesions in the lungs. In the spinal cord there was degeneration of an occasional anterior horn cell, œdema of the sensory roots, and also of the myelin sheath of the sciatic nerve, which is a very early stage in the degeneration of the nerve.

Greenfield and Paterson[13] in this country were the first to make a thorough examination of the nervous system in pink disease. Their cases are especially important from the point of view of comparison between complicated and uncomplicated cases. One case was uncomplicated

and recovery was slowly taking place when the child died suddenly from an intussusception, whilst the other child went slowly downhill and died from generalized tuberculosis. The symptoms of pink disease had been present 3 or 4 months in the first and about 8 months in the second case. In both the same lesions were found in the nervous system, though they were more intense in the long-standing case in which death occurred from tuberculosis. In both cases degeneration of myelin was found in the peripheral nerves of the limbs, more extensive distally than proximally. The vagus and cervical sympathetic nerves were normal. The calf muscles in one case were atrophied, and the small nerve bundles in the substance of the muscle showed degeneration. Above the medulla the nervous system appeared normal. A diffuse infiltration with small cells, which the authors considered to be glial rather than hæmatogenous, was present in the spinal cord in both cases, particularly in the lumbo-sacral region, and there was also an increase of the cellular elements in the nerve roots in the same area. In the more chronic case, especially in the cervical and lumbo-sacral region, the ventral horn cells showed an 'axonal reaction' with central chromatolysis, eccentricity of the nucleus and vacuolation of the cytoplasm.

Feer[9] reported one case with an autopsy. His case was complicated by a terminal broncho-pneumonia, and post mortem the lesions of that condition only were found. The spinal cord and sympathetic system were examined, but not the peripheral nerves.

Butler[15] performed a biopsy and removed a piece of skin from the hand of one case. His description of the skin lesion is of interest. He found hyperkeratosis with ballooning of the cells of the granular layer, and lymphocytic infiltration of the corium with much œdema. He pointed out that nothing in this report was pathognomonic of pink disease, although the outstanding feature, the œdema of the corium, is an unusual finding.

Warthin[16] made a complete examination of two cases in which the cause of death was broncho-pneumonia. He also gave a detailed description of the skin lesion. In both cases the skin showed hyperkeratosis with a scaly desquamation of the horny layer. The papillæ were enlarged, and the perivascular reticulo-endothelium was hyperplastic, but there was no cellular infiltration and only slight œdema. The sweat glands were dilated and hypertrophic, and the sebaceous glands were very small. In the thymus the lymphoid tissue was atrophied and the germ centres in the spleen showed lymphoid exhaustion. The pituitary and pineal glands were normal. The only changes which Warthin found in the nervous system were proliferation of the reticulo-endothelial cells in the cerebral meninges, and congestion of the meninges and brain substance.

Francioni and Vigi[17] recorded an interesting case, that of a child of four and a half years who developed pink disease within a few weeks of an attack of epidemic encephalitis. The autopsy and subsequent microscopical investigation revealed the typical appearances of epidemic encephalitis with, in addition, an infiltration of the cervical sympathetic ganglia with small lymphocytes. No peripheral nerves were examined. The views of the authors on the interpretation of their findings in this case will be referred to later in discussing the theories of pathogenesis.

Kernohan and Kennedy[18] examined in great detail a case in which the cause of death was broncho-pneumonia. The visceral changes were solely those associated with the terminal condition. In the nervous system they describe extensive degenerative changes. These are especially striking as the recorded duration of symptoms was only three weeks. The Marchi method demonstrated myelin degeneration in the femoral and sciatic nerves, and a little also in the brachial plexus. In the sacral, and to a less extent in the lumbar region of the cord, chromatolysis of the ventro-lateral group of anterior horn cells was evident. Varying degrees of chromatolysis were recorded in the cells of the dorsal root ganglia, particularly in those from the lumbar region. The changes varied from slight eccentricity of the nucleus and loss of Nissl granules to complete disintegration of cells. In the brain chromatolytic changes were found in the cells of the eminentia teres, the mesencephalic root of the fifth nerve, the locus cæruleus, the lenticular nuclei and in the anterior thalamic nuclei. The cells of the Gasserian ganglia also showed extensive chromatolytic changes. Some of these findings are undoubtedly open to criticism for reasons which will shortly be mentioned.

Findlay and Stern[19] who produced in rats a condition clinically and pathologically resembling pink disease also published a report of the pathological investigation of a typical mild case of the

disease. The child died from tuberculous broncho-pneumonia. On histological examination the viscera showed only the lesions attributable to that complication. In the nervous system, however, there was found a diffuse infiltration with small round cells, most evident in the cervical region and in the lumbo-sacral enlargement. The infiltration extended along the posterior nerve roots, but the anterior nerve roots were unaffected. A similar infiltration was seen in the medulla. Early chromatolytic changes were present in the eighth cervical segment and in the dorso-lumbar enlargement, and early myelin degeneration was found in the sciatic nerves. The cervical and abdominal sympathetic ganglia and the carotid ganglia were normal. No abnormalities were detected in the muscles, and the intramuscular nerve fibres appeared healthy.

The histological examination of our seven cases of pink disease does not present any new features. It merely confirms those which have already been recorded, and serves to illustrate that lesions in the nervous system occur in a high proportion of cases. Degenerative changes were found in the peripheral nerves in four out of seven cases. In one case of very long standing (Case 1), myelin degeneration had reached such an advanced stage that the Weigert-Pal method was applicable. In another case (Case 7), an interesting feature was present. The child died suddenly of heart failure after a short illness, and the only nerve in which degeneration was found was the vagus.

The spinal cords in all seven cases showed the diffuse infiltration with small cells first described by Paterson and Greenfield. It was very distinct in five cases and slight in the other two. We were unable to determine the nature of the infiltrating cells. They resemble glial cells rather than lymphocytes in their staining reactions, but we could not demonstrate processes on them by either neuroglial or microglial staining methods.

Chromatolysis of the central type was found in the anterior horn cells of the spinal cord in five cases and it was more apparent in the lumbo-sacral region than elsewhere. It was extensive in the most chronic case and was clearly due to an 'axonal reaction.'

Slight changes in the muscles were observed in two cases. These changes were those of a simple atrophy consequent upon a neural lesion.

In only two cases could we detect any abnormality in the nervous system above the level of the medulla. In Case 2 a slight cellular infiltration was present in sections of the cerebral cortex, brain stem and medulla; in Case 3 a similar infiltration was present in the cerebral cortex and the basal ganglia. In the other cases the infiltration was confined to the spinal cord and nerve roots. The cortex, mid-brain, pons and medulla were carefully sectioned for evidence of chromatolysis of nerve cells, but with negative results.

Discussion.—From a consideration of the foregoing pathological examinations the essential lesions in pink disease would appear to lie in the skin and in the nervous system. The lesion in the skin is, according to Butler, not pathognomonic. He described exactly similar changes in the skin in a case of acromegaly. In the nervous system, the evidence for a characteristic and pathognomonic lesion is somewhat meagre, but in the majority of cases in which the peripheral nerves have been examined, evidence of some degenerative change has been forthcoming.

Chromatolytic changes in the anterior horn cells of the spinal cord may be due to a large number of causes, but the fact that these changes in pink

disease occur in the spinal segments corresponding to the nerve supply to the limbs suggests that such chromatolytic changes are due solely to an ' axonal reaction.' The significance of the cellular infiltration of the spinal cord and nerve roots which occurs in a proportion of cases cannot as yet be explained.

The association of a cellular (lymphocytic) infiltration of the cervical sympathetic ganglia with the characteristic changes of epidemic encephalitis in the mid-brain, which Francioni and Vigi described in their case, is of interest in view of the theories of pathogenesis to be mentioned later.

The extensive chromatolytic changes in certain nerve cells which Kernohan and Kennedy described call for some comment. Those changes which were observed in the anterior horn cells of the spinal cord and in the spinal ganglia may be accepted without reserve, and form a valuable addition to our knowledge of the lesions in pink disease. The chromatolysis, however, described in other parts of the nervous system, particularly in the cells of the eminentia teres, the mesencephalic root of the fifth nerve and in the thalamic nuclei cannot be so accepted. Nerve cells in these areas of the brain in a normal subject were subjected by us to a careful scrutiny and we were unable to convince ourselves that rounded cell bodies, eccentric nuclei and peripherally placed or clumped Nissl granules were not normal to cells in these situations. We also referred to the volume on the nervous system in the recent ' Handbuch der Microscopischen Anatomie der Menschen,' in which the descriptions and pictures of cells in the areas of the brain under consideration confirmed our observations that the cells in these areas do not conform to the common type of pyramidal nerve cell with a central nucleus and evenly distributed Nissl granules. We suggest, therefore, that until further evidence of the degenerative changes which Kernohan and Kennedy have described in scattered areas of the brain is brought forward, the question whether these changes should be accepted as part of the pathological picture of pink disease should be left open. We were unable to confirm their results from examination of our own cases.

It is here convenient to summarize the chief clinical and pathological features of our seven fatal cases :—

Case 1.—J. N., female, aged 2 years 7 months. Duration of illness 8 months. No prodromal symptoms. Knee jerks absent. Cellular infiltration of spinal cord. Degeneration of peripheral nerves.

Case 2.—P. E., female, aged 7 months. Duration of illness 2 months. No prodromal symptoms. Knee jerks present. Cellular infiltration of cerebral cortex, brain stem, medulla and cord. No degeneration of peripheral nerves.

Case 3.—M. B., female, aged 1 year, 11 months. Duration of illness 6 months. Knee jerks absent. Prodromal diarrhœa. Cellular infiltration of cerebral cortex, basal ganglia and spinal cord. Degeneration of peripheral nerves.

Case 4.—P. M., female, aged 9 months. Duration of illness 3 months. Knee jerks present. No prodromal symptoms. Died suddenly with rapid pulse. Cellular infiltration of the spinal cord. No degeneration of peripheral nerves.

Case 5.—R. S., male, aged 7 months. Duration of illness five weeks. No prodromal symptoms. Knee jerks present. Cellular infiltration of the spinal cord. Degeneration of peripheral nerves.

Case 6.—B. G., female, aged 7 months. Duration of illness 2 months. Prodromal

symptoms, looseness of motions. Knee jerks present. Cellular infiltration of spinal cord. Degeneration of peripheral nerves.

Case 7.—D. B., male, aged 1 year 3 months. Duration of illness 1 month. No prodromal symptoms. Knee jerks present. Cellular infiltration of spinal cord. No degeneration of peripheral nerves, but degeneration in vagus nerve.

Summary.—A point which appears to need comment is that in all these cases the clinical symptoms were much in excess of the pathological findings, although cellular infiltration was present in all seven and degeneration of peripheral nerves was found in four. Two children died suddenly with a rapid pulse which suggested vagal inhibition. In one of these (Case 7), the vagus nerve were examined and found to be degenerating. The only prodromal symptom observed was diarrhœa, which occurred in two cases. Case 5 is of particular interest in view of the short history (five weeks) and the pathological finding of degeneration in the peripheral nerves.

Pathogenesis.

Soon after the recognition of the clinical entity which we now call pink disease, two theories of its pathogenesis were advocated. One that the condition was consequent upon an unknown vitamin deficiency, and the other that it was the sequel to an infection whose nature and portal of entry were as yet undetermined. Wood in his earlier paper (1921) did not, even on the basis of his ninety-one cases, venture to give an opinion on one or the other of these theories, but in a later communication[20] (1927) he had come to the conclusion that the disease was not an avitaminosis. He agreed, however, with Warthin that the condition was closely related to pellagra, or that it might be an infantile form of that disease. Goldberg's work on pellagra and its causation from deficiency of vitamin B2 had not at that time been published. For this reason it may be assumed that Wood subscribes to the avitaminosis theory rather than to the theory of an infective origin. Others who maintain that pink disease is due to a vitamin deficiency are McClendon[21] and Zahorsky[22], both of whom claimed good results from treatment with yeast and irradiated ergosterol.

A view slightly divergent from the avitaminosis theory is held by Findlay and Stern[19] who, as the result of experimental work on rats suggest that the absence of a dietetic factor other than the known vitamins is responsible for the causation of pink disease. They produced a condition in young rats clinically resembling pink disease by feeding them with dried egg white as their sole source of protein, the rest of the diet being adequate and rich in vitamins. The same condition was produced in breast-fed rats by feeding the mothers on a similar diet. Cultures from the affected animals were negative. Attempts to reproduce the disease by means of intraperitoneal or intracerebral injection of blood or emulsions of the spinal cord from the affected animals were unsuccessful. Pathologically, degenerative changes were found in the peripheral nerves and the same curious cellular infiltration of the spinal cord that has been described in pink disease was observed in the cords of the rats.

Although the formation of a toxic substance during the drying of the egg white must be considered as a possible positive factor, the experimental evidence certainly suggested that an essential factor in the diet was lacking, especially as the condition was rapidly cured by the addition of raw liver to the diet. The authors tentatively suggested that if the condition which they produced experimentally was identical with pink disease, then a dietetic factor in addition to the known vitamins is necessary for normal nutrition in the young child.

The consensus of opinion, however, in this country, in America and in France, is that pink disease is due to an infection. Paterson and Greenfield[14] were the first to bring forward that theory in England, although Byfield had previously drawn attention to the similarity of the polyneuritic changes in pink disease to those in post-influenzal polyneuritis and radiculitis.

Rodda[23], in support of the infective theory, maintained that he had never seen a case of pink disease in which there had not been a previous focal infection of the upper respiratory tract. Vipond[24], Péhu and Ardisson[25], Littlejohn[4], and Kernohan and Kennedy[18], also regarded the naso-pharynx as the portal of entry of the infective agent. Kernohan and Kennedy considered that the changes in the nervous system, which they described, were toxic in origin, secondary to dissemination of the products of the infective agent throughout the body.

The nature of the infective agent has been the subject of much speculation, especially in France. Janet[26] and Turquety[27] maintained that the infection was probably due to a neurotrophic virus, which Janet thought was allied to the virus of epidemic encephalitis, although Turquety did not agree with this view. Both these authors considered that the virus gained access to the nervous system through the naso-pharynx, and that it probably exerted its effects on the vegetative centres in the mid-brain.

Francioni and Vigi[17], to whose paper reference has been made, were also of the opinion that pink disease was due to a neurotrophic virus which entered the nervous system through the naso-pharynx. They believed that the virus was either identical with, or closely allied to, that which produces epidemic encephalitis, and that definite and unmistakable lesions were produced in the vegetative centres of the infundibular region. Their case in which pink disease developed a few weeks after a typical attack of epidemic encephalitis certainly had lesions in these centres as well as cellular infiltration of the cervical sympathetic ganglia. It is, however, premature to base a theory on one such case, as the lesions of epidemic encephalitis itself may be scattered throughout the nervous system and despite the ubiquity of epidemic encephalitis, theirs is the first and only case we have been able to trace in the literature in which the symptoms of pink disease have been associated with an attack of epidemic encephalitis. Further pathological evidence, therefore, is needed before the theory of a neurotrophic virus allied to that of epidemic encephalitis can be seriously considered as the cause of pink disease.

A theory which has received scant attention as yet, but which accords well with the mass of clinical evidence, is that brought forward by Feer and Selter in Germany. Both these authors regarded the condition as a

'trophodermatoneurosis,' dependent upon a dysfunction of the vegetative nervous system. They instanced the cold clammy extremities, the sweating, the rapid pulse, the high blood pressure and the irritability of the affected children as evidence of a disturbance of the sympathetic system and compare the rash with those of other known dermato-neuroses. Feer had the sympathetic system 'examined minutely' in a fatal case of pink disease, but no organic changes were found. He therefore came to the conclusion that the condition was due to a disturbance of function and not to one of structure. This theory is worthy of more attention in view of the fact that the structural changes in the nervous system are often slight in comparison to the severity of the clinical symptoms.

Which of the various theories of pathogenesis best explains the production of the lesions in the nervous system is a difficult question to answer. A deficiency of any of the known vitamins can be excluded as the cause, as in most cases, in which the diet has been investigated, they have been present in adequate quantity. Cases with prodromal symptoms of pharyngeal or intestinal catarrh favour an infective origin, but in numerous instances, as in several of our own cases, no history of preceding infection could be elicited. In none of our cases was there any evidence of an inflammatory cervical adenitis.

Treatment by liver.

With a special diet, already referred to, Findlay and Stern[19] (1929) were able to produce in young rats a syndrome resembling pink disease both in its clinical and anatomical aspects. Adult rats had a much greater resistance against the development of the disease, but the milk of female rats so fed caused the disease to appear in their sucklings. By adding raw liver to the diet it was found that the disease in rats could be rapidly cured. Acting on this suggestion of a similarity between the human and animal syndromes, raw liver was given in human cases of pink disease with satisfactory results.

Case 8.—I. W., a female child, aged 1 year and 5 months, breast-fed for four months. The infant had a five months history of irritability, and wasting, with an itchy eruption, sweating and desquamation of the skin. She was miserable, whining, shunning the light, and burrowing her head in the pillow. The hands and feet were typically raw-beef in colour, the eyelids were inflamed, nasal discharge was present, and there were numerous septic sores on the hands and feet. The pulse rate was 125 to 140, the systolic blood pressure 110 mm., and the temperature normal. Analgesia was present as tested by pin-prick, the knee jerks were absent, and the muscles extremely hypotonic.

Raw liver, two ounces pounded and mixed with milk, or with a drachm of port-wine to the ounce, was added to the diet as a daily ration. Within a week a remarkable change occurred. The child was able to sit up in bed, contented, taking notice, and photophobia was much less. The rash disappeared, and the inflammation of the eyelids and the septic sores on the hands and feet quickly healed. The swelling and the raw-beef colour of the hands and feet were much improved. It appeared that the activity of the disease had become arrested, though several more weeks elapsed before a slight residual cyanosis of the hands and feet disappeared. The child was kept under observation for six weeks on liver diet. When discharged the knee jerks were still absent, but the child was otherwise in good health.

Case 9.—J. S., a female child, aged 7 months, and breast-fed. There was an eight weeks history of anorexia, loss of weight, irritability, photophobia, profuse sweating, and an erythematous rash on the hands and feet. The knee jerks were absent, and there was no sensory impairment.

Raw liver, one ounce a day, was given. On the fifth day of treatment there was some improvement, on the ninth day the child was definitely better, and on the twentieth day only some hypotonia of the muscles and slight cyanosis of the hands remained.

Case 10.—M. R., a female child, aged 1 year and 4 months, breast-fed for nine months. For four months the infant had been miserable, wasting, without appetite, avoiding the light, and sweating profusely. The muscles were hypotonic and the hands and feet a typical raw-beef colour and very cold. There had been no respiratory catarrh. The pulse rate was between 110 and 140, and the temperature normal. The knee jerks were obtained with difficulty.

The case is interesting because an attempt was made to give the liver treatment at home. Raw liver, 2½ ounces, was ordered to be given daily, and in 3 months no improvement had occurred. The treatment had apparently completely failed, but as considerable doubt existed whether instructions had been properly and regularly carried out, the child was admitted to hospital for a further trial. Raw liver, 2 ounces daily, was then given for 14 days, in which period the child became cheerful and all the symptoms disappeared except slight photophobia and a little duskiness of the hands and feet. As improvement occurred, the cyanosis of the extremities became phasic, coming and going in the hands and feet several times in the same day.

The effect of liver treatment in this case is doubtful, as the child might have been expected to recover spontaneously in eight months, yet the rapidity with which the symptoms improved while under observation on liver treatment was very noticeable.

Case 11.—H. M., a male child, aged 7 months, cut two teeth at five months. At five months the infant became miserable, crying continually, without appetite, and losing weight. In bed he assumed the knee-elbow position with the head burrowed in the pillow. Nasal catarrh, photophobia, sweating, and coldness and redness of the hands and feet were present. Pulse rate 115 to 130, temperature normal, knee jerks present.

30.1.31. Raw liver, 2 ounces daily, mixed with milk and flavoured with sugar, was commenced. Weight: 12 lb. 11 oz.

14.2.31. Erythema of feet and hands improved. Photophobia much less. Disposition more contented. Weight: 13 lb. 4 oz.

4.3.31. Pink condition much improved.

13.3.31. Complete recovery. Weight: 14 lb.

Recovery in this case took place in 6 weeks, which was at a slower rate than in Cases 1 and 2.

Case 12.—A. S., a female child, aged 5 years and 10 months (Dr. Cockayne's case). This child was not admitted to hospital and only seen at fortnightly intervals.

There was a three weeks history of pains in the limbs, hands, groins and jaws. The child was miserable and losing weight.

4.9.30. Temperature 99·4°. No physical signs of disease were found.

25.9.30. The child was very miserable, restless, and complained of pains in the hands. A miliary rash was present on the lower part of the trunk, and the feet and hands were cold and raw-beef colour. There was general muscular atony, and the knee-jerks were absent. The appearances were typical of pink disease.

From this date, liver soup, half a pint a day, was commenced. When next seen, fourteen days later (9.10.30), the child was much better, less irritable, and sleeping well. The colour of the extremities had improved and they were no longer cold. The left knee jerk was present, but feeble. The right knee jerk absent.

23.10.30. There was no evidence of pink disease present, except that the right knee jerk was still absent.

A subsequent note five months after the child first came under observation reads that both knee jerks were obtainable, but diminished.

While these five cases were under observation, no other special form of treatment was given. Cod-liver oil and orange juice were included in the diet,

but had already been given at home in the two infants aged seven months. In previous cases we have never seen any material benefit occur from the inclusion in the diet of substances containing any of the known vitamins A, B, C, and D.

The fairly rapid improvement witnessed in Cases 8, 9, 11 and 12 speaks well, in our opinion, for liver therapy. It appeared to arrest the activity of the disease within a short time, a week to fourteen days, although a considerably longer period is necessary for such signs as the cyanosis of the extremities and the photophobia completely to disappear. A return of the knee jerks, as might well be expected, was delayed the longest. One of the earliest effects of liver therapy was a noticeable improvement in the general condition of the patient: the irritability and pain apparently quickly subsided. None of the cases relapsed.

Five cases is too small a number on which to base emphatic views, but from the results we have obtained with liver therapy, we submit that a dietetic factor contained in liver has a definite value in curing the disease. Of the nature of this factor, and whether a deficiency of it can cause the disease in the absence of a positive factor, possibly infective, we are at present unable to judge.

We desire to express our thanks to members of the honorary staff of the Hospital for Sick Children, Great Ormond Street, for placing the pathological material at our disposal and for their permission to publish the cases; to Dr. Paterson and Dr. Sheldon for two cases from Westminster and King's College Hospitals respectively. Finally, we wish to thank Dr. J. Godwin Greenfield for granting us facilities for studying our material in the laboratory of the National Hospital, Queen Square, for his interest in the work, and for kindly taking the microphotographs.

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MALIGNANT HYPERTENSION IN CHILDHOOD

BY

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Essential hypertension is predominantly a disease of the later years of life. It is uncommon under thirty years, and rare in childhood. Two forms or phases have been described, the benign[6, 7] and the malignant. There seems to be unanimity of opinion among the writers on the subject regarding the clinical differentiation of the two forms, but the pathogenesis of the malignant type is still open to dispute. This type is usually seen in relatively young people, the average age being about forty.

Cases in children have been recorded by Keith, Wagener, and Kernohan[1], by Amberg[2], by Klemperer and Otani[3], and by Murphy and Grill[4].

In this article we describe the malignant hypertension syndrome and the autopsy findings in a girl of eight, who was observed over a period of eleven months.

Clinical report.

A. D., female, aged 8 years, was admitted to hospital on January 29th, 1930, in an unconscious condition. The evening before admission, she had gone to bed as usual about 7 p.m., but had wakened screaming at 10 p.m., and had cried off and on all night. At 7 a.m. she had complained of severe frontal headache, staring into space and complaining that she could not see anything. At 9 a.m. she had had a fit with jerking of the face and eye-balls, movements of the arms, and blueness of the face. The fit had lasted twenty minutes. Half an hour after this, she had had a second similar fit, and was then admitted to hospital.

She was born at full term, after a breech presentation and a protracted labour. When two days old, she vomited blood, and also passed blood per rectum. This went on for several days and stopped without any special treatment. At the age of two, several days after her sister had been removed to hospital with scarlet fever, she had a sore throat of a dubious character and vomiting, but without any rash. She had whooping cough at three years, but never had measles. She was nearly two years old before she walked and talked.

She was never a strong child, and always seemed a little behind girls of her own age. 'Almost from the time she could speak' she had every other week a frontal headache, which was sometimes followed by vomiting. During the year previous to admission, the headaches came about twice a week, and during the previous week she had an attack every morning. The headaches were almost always in the morning, beginning about 7 a.m. and disappearing in the course of the forenoon. From time to time the child had attacks of inexplicable irritability. Nose bleeding had occurred a few times in the year before admission.

The father and mother, aged 48 and 39, are alive and well. The former had nephritis at the age of 14, but has now a normal blood pressure and no albuminuria. A sister aged 10, and two brothers aged 6 and 1½ are well, and have no signs of vascular or renal disease. No history was forthcoming of any family tendency to vascular disease at an early age.

On admission the child had several short fits. She remained unconscious. She was pale and looked ill. There was no œdema. The heart was overacting, with the apex beat just outside the nipple line. The first sound at the mitral was loud. The second sound at all areas

was accentuated, and specially so at the aortic. The child looked like a case of meningitis. She lay with her back arched and her legs curled up and was restless and resisted handling. There was slight rigidity of the neck. There was hemiplegia of left arm and leg. The right plantar reflex was flexor, the left was extensor. No clonus was elicited. Both knee jerks were exaggerated, the left being greater than the right. On lumbar puncture, the cerebro-spinal fluid was under pressure, and showed an increase in globulin, and a fine coagulum developed on standing. The cells numbered 3 per c.mm., and no micro-organisms were found. The temperature was 102·8°, and the pulse rate 150. Nothing abnormal was found in the lungs or abdomen.

COURSE.—The following morning the child was quieter. The blood pressure was estimated, and found to be 160/120. The fundi of the eyes were examined and showed a hypertensive retinopathy[5]. The report stated that the edges of the discs were blurred from slight swelling, the retinal arteries were tortuous, and the veins engorged. Several white woolly patches were seen in both eyes, and small white dots arranged in lines radiating from each macula. Numerous scattered small hæmorrhages were seen in both eyes and in the right there were coarse flame hæmorrhages among the superior temporal vessels, not far from the disc.

As the child was still unconscious hypertonic saline was given intravenously, after which she became less restless and began to take fluids by mouth. The temperature came down steadily, as did the pulse rate, and by the morning of the second day after admission the girl was conscious and could see, and had regained power in the left arm and leg. Thereafter she steadily improved. The urine contained rather more than a trace of albumin, no sugar, and a few pus cells, but no red blood cells and no casts. The albumin decreased to a mere trace within a fortnight. The specific gravity during the first month varied in different samples from 1010 to 1025. There was no upset of the normal day to night ratio, and no nocturnal frequency of micturition. The blood urea on February 4th, despite occasional vomiting and some dehydration, was only 46 mgrm. per cent. Cerebrospinal fluid was again withdrawn on February 9th; it was not under pressure, and was normal as regards cells and protein. The urea of this fluid was 29 mgrm. per cent.

The child weighed 33 lb. and was 44½ in. in height. She was thin and pale. There were no clinical or radiographic signs of rickets. The X-ray examination of the skull showed a normal sella turcica. The tonsils were ragged, and the tonsillar glands slightly enlarged. There was a catarrhal condition of the nose, but no chronic sinus suppuration. Throat and nose swabs gave only the usual catarrhal organisms. No diphtheria bacilli were found on repeated examination. The Wassermann reaction of the blood was negative.

The urine was kept alkaline with potassium citrate, given in five doses daily of 25 grn. each. The bowels were kept well open. On February 15th, the blood urea was 42 mgrm. per cent.

She went on improving for five weeks, although the blood pressure remained around 160/120. The urine remained as before, and there was morning headache from time to time.

Then in the first week of March came the next series of dramatic symptoms. Sickness and vomiting occurred every morning. On March 6th, the frontal headache was very severe in the morning, and the child was very sick. Later in the day she had four convulsions within an hour, and became unconscious. Lumbar puncture yielded fluid under great pressure. It was colourless, and the globulin was increased. The urea of the fluid was 50 mgrm. per cent. The cells were not increased, and no micro-organisms were found. The temperature was normal. Hypertonic salines were given. She remained semi-conscious for forty-eight hours, and did not appear to see. She vomited often, and the temperature rose to 102°. It fell steadily to normal next day, and the child improved slowly. The urine contained albumin, but no blood and no casts. The systolic blood pressure was 160; it was impossible to estimate the diastolic pressure accurately. The interesting point was noted then that punctate hæmorrhages were produced in the arm by the armlet of the sphygmomanometer. The blood urea on March 7th was 86 mgrm. per cent. The eye report then read: 'Discs still show blurring of the edges. There are hæmorrhages as before and radiating dots round the maculæ, but no woolly patches can be seen.' On March 10th the urine became red, and deposit showed red blood cells, a few pus cells, and blood casts for a few days.

Unfortunately, on March 12th virulent diphtheria bacilli were obtained from the nose and the child had to be transferred to a fever hospital, where she remained for five weeks. After this she remained at home for about two months, in fair health, but with frequent headaches and vomiting.

RE-ADMISSION.—On June 16th she was re-admitted to hospital. She was still pale, poorly nourished, and weighed 35 lb. The blood pressure was 210/150. The fundi of the eyes showed swelling of the discs, radiating dots around the maculæ, sclerosis of the vessels and a few small hæmorrhages. The blood urea was 48 mgrm. per cent. The urine varied in specific gravity from 1010 to 1020; it contained 0·1 to 0·2 per cent. of albumin, and the deposit showed a few red blood cells and pus cells, and B. coli, but no casts. The serum calcium was 10·2 mgrm. per cent., and the plasma phosphates 4·2 mgrm. per cent. The blood continued in the urine for a week. She continued to have, almost every morning, a severe headache, usually followed by vomiting, and for the next month was otherwise in fair health. Eye examination on July 17th showed the retinal hæmorrhages to have disappeared, and the blurring of the discs to be less marked. The radiating dots at the maculæ remained.

On July 20th came the next alarming group of symptoms. Along with severe and continued headache came absolute loss of vision. After seven hours of this she had a convulsion and became unconscious. She remained so for 24 hours, and during this time had five fits of a generalized type, and the temperature rose to 102·4°. Lumbar puncture was done, and the fluid, which was under pressure, contained a moderate increase in globulin, but no increase in cells. The child improved steadily on the third day of this acute phase, the temperature became normal, consciousness returned, but it was only the following day that the child could see. On July 24th and 25th blood and a little mucus appeared in the stools, and no pathogenic micro-organisms were found.

The child continued to have headache and sickness every other day. On August 29th, the blood urea was 40 mgrm. per cent. and the blood pressure 220/150. The daily amounts of urine during the illness varied from 17 to 42 oz., and the specific gravity from 1008 to 1024. There was no nocturnal frequency. A blood count on September 15th showed 90 per cent. hæmoglobin, 4,600,000 red cells, and 7,200 white cells. There was nothing of note in the character of the cells.

A urea concentration test, after 10 grm. of urea, showed the following percentages of urea in the urine at hourly intervals:—0·9, 0·7, 1·0, and 0·9.

The next episode of note in the case came on September 27th, when complete paralysis of the external rectus muscle of the left eye was observed when the ward sister came on duty in the morning. At this time the nervous system was otherwise normal, and the eye report was: 'Retinal vessels are tortuous in places with here and there increased brightness of light reflex. Right optic disc is more blurred than it was six weeks previously. Small white spots are seen at nasal side of right disc, and at right macula. The superior temporal vessels disappear a short distance from the optic disc in a red grey region. The left optic disc is paler and clearer than the right. White spots are seen around the macula. No hæmorrhages are seen in either eye.' The paralysis of the left external rectus muscle took about eight weeks to clear up.

Except for headaches the child remained fairly well during October and most of November, the systolic pressure being around 220 and the diastolic around 150. Then on November 24th she complained of loss of sight, became unconscious, and that day had six generalized convulsions. Lumbar puncture yielded a fluid under pressure, colourless, with a moderate increase in globulin, and no increase in cells. Its urea content was 57 mgrm. per cent. The child remained semi-conscious for forty-eight hours, with staring eyes, and occasional vomiting. The systolic pressure during the attack was 230 to 240.

Improvement after this attack of unconsciousness was slow, and the headaches became more frequent. The urine albumin increased to 0·3 per cent., and during the first week of December the urine contained red blood cells, but no casts. Fresh hæmorrhages were noted in the retinæ in December. The highest specific gravities in the 24-hour samples of urine in the twelve weeks preceding death were in order: 1012, 1022, 1015, 1018, 1020, 1022, 1020, 1022, 1018, 1015, 1012 and 1015.

On December 13th, she had what appeared to be an attack of angina pectoris, and after it said she could hardly breathe, as there was a weight pressing on her chest. On the 16th she became semi-conscious, and had a fit with movements of the right side of body, and nystagmoid jerkings of the eyes to the right. Later that day she had two more fits, one generalized and one with movements of the left side. The systolic pressure was then 250, and the diastolic probably 150. She vomited food repeatedly. The cerebrospinal fluid was under pressure, its globulin was again increased, there were 12 cells per c.mm., and the urea content was 120 mgrm. per cent. The apex beat of the heart was by this time half an inch outside the nipple line.

The child went steadily downhill after this last acute phase. She was never fully conscious, and was at times pale and collapsed. By the 19th December, the blood pressure had fallen to 170/140, and œdema appeared in the legs. The tongue became foul and coated. That day breathing became laboured and signs of pneumonia appeared at the left base, and the temperature reached 101·6°. By the 24th the apex beat was 1½ in. outside the nipple line. There were tremors from time to time, but no convulsions, and no paralysis. Death took place on the 25th December, apparently from uræmia, pneumonia and cardiac failure.

Post-mortem report.

Post mortem on December 25th. Permission for abdominal incision only. The stomach was of normal size. Its mucosa was slightly inflamed and covered with a film of blood-stained mucus. No erosions or ulcers. Duodenum healthy. Small and large intestines normal. Appendix healthy. Mesentery of small intestine showed several small caseous glands. No naked eye alterations in the mesenteric vessels. Spleen weighed 105 grm. and showed no changes on surface or on section, and there were no visible changes in the vessels. Pancreas normal. Suprarenals were normal in size and appearance. Liver, pale, weighing 895 grm., showed fatty change, and no naked eye alterations in its vessels. Gall-bladder normal, and bile ducts patent. Uterus, tubes and ovaries healthy.

There was a moderate amount of fluid in the peritoneal cavity, and in both pleural cavities, but no excess in the pericardial sac.

Both lungs were congested. The lower lobe of the left lung was completely consolidated and showed the grey hepatization of lobar pneumonia. There were some petechial hæmorrhages into the pleura over the consolidated lobe. The pericardium was healthy. The right auricle was dilated. There was slight dilatation and hypertrophy of the right ventricle. The tricuspid and pulmonary valves were healthy. The left auricle was very definitely hypertrophied. There was great hypertrophy and moderate dilatation of the left ventricle. There was some uniform arteriosclerotic thickening of all the larger branches of the coronary arteries. The mitral cusps were healthy, save for one or two superficial yellow flecks of early atheroma on the aortic aspect of the aortic leaflet of the valve. There was a trace of atheromatous thickening of the extreme bases of the aortic cusps. The ascending aorta was slightly dilated and showed a little superficial fatty change. There was some atheroma of the abdominal aorta, mostly localized to a strip, about an inch wide, involving the whole circumference at the middle of the aorta.

KIDNEYS.—Left kidney much reduced in size and weighing 34 grm. Very distorted contour, the kidney being much narrower opposite the hilum. Capsule not thickened and stripped fairly readily. Outer surface pale in colour, almost smooth, but on close examination showed a number of very fine red and evidently vascular depressions. The narrowed part opposite the hilum was smoothly depressed and had the appearance of vascular connective tissue. The cut surface showed extreme narrowing of the cortex, which in places, e.g., opposite the hilum, was little more than 1 mm. thick. Surface of cortex pale. At one point in cortex there was a small cyst 3 mm. in diameter. The medulla was deeply congested, reduced in size, and its demarcation from the cortex remained clear. The tips of the pyramids projected normally into the pelvis, but a few were flattened. The pelvis of the ureter was of normal size, but there were petechial hæmorrhages into its mucosa. The tips of the pyramids were slightly hæmorrhagic. There was no increase in the peri-pelvic fat.

Right kidney of about normal size, and weighed 84 grm. Capsule not thickened, and stripped readily, leaving a practically smooth, pale surface studded with numerous petechial hæmorrhages. The cut surface showed a cortex of normal width and pale and blotchy in colour. At its upper pole was an irregular wedge of a dead-white colour and apparently partly necrotic. The medulla was well demarcated from the cortex. There was again a hæmorrhagic condition of the tips of the pyramids.

In neither kidney was there obvious prominence of the vessels on the cut surface. The ureters were of normal calibre. There was no obstruction to the flow from either ureter into the bladder, nor in the urethra, and the bladder wall was not hypertrophied. There was no cystitis, but the trigone was congested and showed petechial hæmorrhages.

MICROSCOPIC EXAMINATION.—LEFT KIDNEY. (A). Section of depressed area opposite hilus. The vessels, medulla, and cortex will be described in order.

Vessels. The larger of the arteries in the section, middle-sized arteries, showed but one change, a hypertrophy of the media, sometimes slight, at other places considerable, but always present. There were no fatty or other degenerative changes, and no inflammatory change. The intima and adventitia were unaltered, and the elastic tissue was normal in distribution, there being only slight thickening of the internal and external laminæ.

In the arterioles, and arteries of slightly larger calibre, diverse severe changes were found. Transitions between the different appearances found were so numerous and so close-set as to establish the view that they represented successive stages of the same lesion. Such changes were :—(1) Some vessels showed no more than a thickening of their wall, and narrowing of the lumen, due entirely to an extreme hypertrophy of the media. (2) In other vessels similar medial changes were present, but, in addition, a hyaline and fatty thickening of the intima, without cells, had taken place round a part or whole of the circumference. Adventitial changes were absent. (3) In many vessels, the lumen was completely closed by a marked acellular hyaline

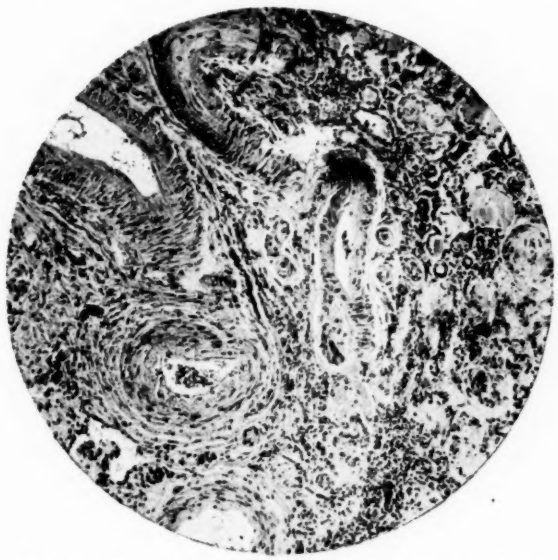

FIG. 1. Section (low power) of atrophied part of kidney, to show vessel changes.

fatty thickening of the intima. Outside this, in the larger vessels of this group, there was a thinned internal elastic lamina, and the media consisted of just a few muscle-cells plastered over the thickened intima. This third type of change was generally more fully developed in the actual arterioles, and the severer grades were particularly common in atrophying areas of cortex.

The veins did not show appreciable alteration. The capillaries everywhere showed marked congestion and over-distension, the intertubular plexus, the capillaries in atrophied cortex, and capillaries in medulla. The walls showed no obvious pathological change, but extravasated red blood corpuscles could be found everywhere.

Medulla. The transitional epithelium covering the pelvis was normal in the portion shown in the section. The tips of the pyramids showed little beyond numerous extravasated red cells. The cells of the interstitium, as is normal here, were scanty, but there were occasional foci of small round cells. Capillaries were congested, and arterioles as above. The lower ends of some collecting tubules had been partly destroyed by the hæmorrhage, and the lumina were filled with blood. Higher up in the pyramids, the collecting tubules were fairly normal, save that they were rather dilated and some contained homogeneous material.

Cortex. The site of entry of vessels between pyramids, and the inter-pyramidal cortex just above that, showed practically nothing but the leash of entering vessels and their branches,

along with a considerable increase of connective tissue with few cells. The number and variety of size of arterial vessels in this small area devoid of tubules, showed that it represented nevertheless most of the inter-pyramidal cortex which had been wiped out by the withering of the vascular tree. The vascular changes varied with the size of the arteries and have already been detailed.

The remainder of the cortex showed one of two appearances. First, part of it, a layer consisting mostly of the deeper part of the superficial cortex, was clearly hyperplastic. The convoluted tubules were enlarged, and lined by swollen epithelium, which was undergoing granular degeneration. There was only a trace of collagenous increase in the interstitium with no infiltrating cells. Many glomeruli were enlarged. Recent parietal capsular epithelial proliferation was present only in one or two tufts. Some glomeruli were partly adherent to their capsules, and one or two were necrotic. Secondly, the superficial layer of the superficial cortex was composed of atrophying parenchyma and glomeruli. The latter were small, hyaline, and close-set. Intimal changes were generally present in the arterioles. There was only a little increase of connective tissue separating the atrophied glomeruli and tubules, and only few cells.

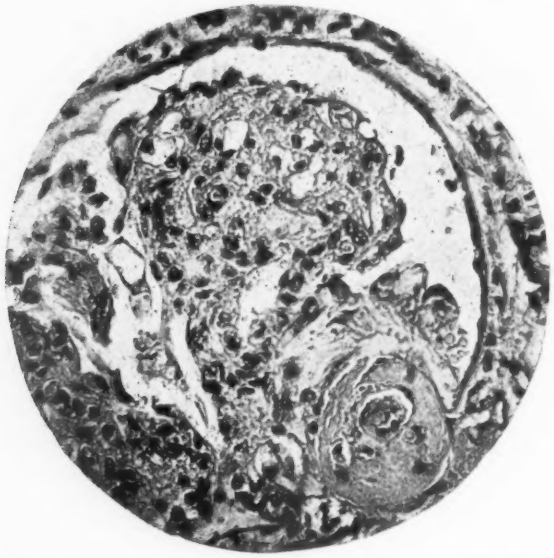

FIG. 2. Section (high power) of glomerulus, showing sclerosis of afferent arteriole.

(B). Section at upper pole. This section showed a fairly thick cortical mantle. Description of the cortex :—

Vessels. The types of change were identical with those described in the first section. No normal arteries or arterioles were seen, and as before, the changes varied with the size of the vessels.

Glomeruli. Only one or two scattered hyaline glomeruli were seen. Many of the remaining ones were enlarged. Hardly any were adherent to their capsules. Occasionally glomeruli were encountered in which the tuft tissue had undergone almost complete necrosis, the capsule containing numerous red cells, and also degenerating endothelial cells. There were no proofs of inflammatory factors in such necrosis.

Tubules. Some patches of convoluted tubules showed great hyperplasia, and granular degeneration. Some tubules were blocked by masses of desquamated cells; others were atrophied, with flat lining epithelium and varying degrees of dilatation of the lumen.

Interstitium. There was a very slight increase amid hyperplastic tubules, and a little more amid atrophied ones. Generally there were few cells in this increase. Capillaries were everywhere congested, and there was extravasation of a few red blood cells into the interstitium, and into a few of the tubules.

RIGHT KIDNEY. (A). Section distant from the specially degenerated upper pole area.

Vessels. These showed the same diversity of changes as in the other kidney. In particular, all the arterioles were seriously altered.

Medulla. Some tubules were fatty, but the most distinct changes were marked capillary and venous congestion, with capillary hæmorrhages, and occasional round-celled infiltration.

Cortex. Only one or two glomeruli were hyaline. The majority were rather large, and showed no epithelial prolifieration. A few whole tufts were completely necrotic. The majority of glomeruli showed only slight changes. Hyperplastic and degenerated convoluted tubules were predominant. Atrophied tubules, such as were described in the other kidney, were also present, but in small numbers. There was more fatty change than in the tubules of the other kidney. Some tubules were completely necrotic.

The interstitium showed practically no increase. The capillaries were again congested, and there were occasional capillary hæmorrhages into the interstitium.

(B). Section of degenerated tissue at upper pole. The degenerative changes were marked in both glomeruli and tubules. About one-half of the glomeruli showed fatty or necrotic changes. Many of the hyperplastic tubules were fatty, most were necrotic.

LIVER.—There was no cellular infiltration of the portal tracts or under the capsule. Most of the arterioles showed a little medial hypertrophy but no further change. None showed appreciable intimal change. There was extensive parenchymatous fatty change, of irregular distribution, although chiefly peripheral and central.

ABDOMINAL AORTA.—The naked-eye changes seen were those of pure nodular atheroma.

SPLEEN.—The Malpighian bodies were of normal size. Practically every central artery and its arteriolar branches showed marked thickening and narrowing, often apparently amounting to closure. The thickening was usually entirely due to a hyaline thickening of intima. Slightly larger arteries in trabeculæ sometimes showed a trace of similar intimal thickening, but the usual change was slight medial hypertrophy. The internal elastic lamina was not thickened.

HEART.—There were a few degenerate fibres, but most were healthy : no abnormal cellular infiltrations, and no fibroid changes. The coronary arteries showed medial hypertrophy. The descending branch of the left coronary showed some hypertrophy of the media, and also moderate uniform fibrous thickening of the intima with few cells and much elastic tissue. Slight medial hypertrophy of some arterioles, although most were healthy.

LEFT LUNG.—The lower lobe showed lobar pneumonia, early grey hepatization. No abnormalities of the vessels of the lung.

BLADDER.—The smallest arteries and arterioles, both in muscle and mucosa, showed medial hypertrophy, and in some arterioles slight hyaline thickening of the intima.

SUPRARENALS.—There was no change in the parenchyma of either cortex or medulla, but in the vessels there was a considerable hyaline thickening, sometimes leading almost to obliteration of the lumen. This was entirely an intimal thickening, the media having completely disappeared. The vessel walls were almost structureless.

HEAD OF PANCREAS.—The tissue of pancreas and islets was healthy. The arterioles practically all showed changes, hyaline thickening of intima with no great narrowing of lumen, slight hyalinization of media, and slight hypertrophy of media. The islets were over numerous(?).

CŒLIAC AXIS.—Hypertrophy of media ; no intimal or advential change.

VOLUNTARY MUSCLE (left rectus abdominalis).—Muscle fibres healthy. Minimal hyaline thickening of intima of some arterioles, others not altered. The arterioles in the fat within the muscle sheath showed slightly greater change, greater intimal thickening. The arteries had only medial hypertrophy.

Summary of autopsy—(a) The typical arteriolar changes of essential hypertension in all the organs examined, except the lungs. In order of severity of changes, the organs were kidneys, spleen, suprarenals, bladder, liver, voluntary and heart muscle. (b) Hypertrophy of large arteries, verified in coronaries, renal arteries and cœliac axis. (c) Atheroma of aorta. (d) Secondary contraction of left kidney. Arteriolo-sclerotic ischæmic atrophies, degenerations and necroses in both kidneys. (e) No nephritic changes. (f) Lobar pneumonia.

Summary.

A case of malignant hypertension is described in a girl of eight years old. The autopsy findings are described in detail.

It will be noted that headaches had been complained of for a number of years, and had persisted to the end. The period of the malignant phase lasted at least a year, and was punctuated by bouts of alarming symptoms: convulsions, cerebral amaurosis, unconsciousness, transient hemiplegia, and paralysis of a sixth cranial nerve. Some renal impairment was present during the period under observation, but only at the very end did it become a pronounced feature. The specific gravity of the urine never became fixed. Blood was passed in the urine from time to time.

The blood pressure rose steadily, and was specially high in at least two of the series of acute exacerbations. The typical picture of hypertensive retinopathy was present all the time, with macular exudates, neuro-retinitis, sclerosis of retinal vessels, and hæmorrhages, while woolly patches were not a feature except at the beginning of the observations. During the unconscious periods, the cerebrospinal fluid was under increased pressure, and on each occasion on which it was examined, it contained an increase in globulin with no increase in cells. In the intervals the fluid was normal.

The clinical diagnosis of malignant hypertension was confirmed at autospy. This revealed the typical arteriolar changes of essential hypertension, and the renal arteriolo-sclerotic atrophies and necroses of the malignant phase of the disease.

I am greatly indebted to Dr. John Gray, pathologist to the hospital, for the report on the naked-eye and microscopic appearances.

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ACUTE AND CHRONIC NON-TUBERCULOUS PYURIA IN CHILDREN

BY

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Bacillus coli infection within the renal tract is of common occurrence in children and like many other disorders the disease may be recognized in an acute or chronic phase. Probably a large number of cases are overlooked, the general disturbance, unless severe, and the urinary abnormality clearing up under simple medicinal methods. Nevertheless there are several points of great importance to be considered in this group of diseases. It is not the writer's intention here to argue or to attempt to prove how the bacilli reach the renal tract initially. Suffice it to say that there are probably two important ways, an ascending urinary tract infection from the urethra or bladder, and by the hæmatogenous route. A lateral spread from such conditions as appendicitis or entero-colonic conditions is unlikely, although B.coli bacteriæmia or septicæmia may so arise and cause infection in the urinary tract. It has recently been shown that so-called catheter fever is due to actual invasion of the blood stream by coliform bacilli after slight urethral trauma. It is remarkable that many of the coliform bacilli possess unusual pathogenic powers when introduced into the urinary tract, and under certain conditions purulent discharge due to these bacteria may prove extremely resistant to treatment, a condition of chronic pyuria resulting.

The observations tendered in this paper are chiefly concerned with a clinical study of about one hundred and thirty cases of pyuria, some of the main questions under consideration being (a) does the so-called acute pyelitis cause any immediate or remote renal damage ? (b) why does the pyuria become chronic in some patients ? (c) what is the treatment of the different types of case ?

During a period of five years (1924-29) one hundred and seventeen cases of pyelitis were admitted to the Children's Hospital, Birmingham. It should be remembered that this number of cases in no way indicates the frequency of the infection in children since many of the milder examples are satisfactorily treated in the out-patient department. Any case of persistent pyuria would necessarily be admitted for further detailed investigation. Therefore it is true that most of the cases studied in this paper have been patients who showed clinical evidence of severe general disorder associated with the urinary findings. Obviously such a large number of cases would show a wide variety of clinical symptoms.

In infants the clinical aspect is that of a moderately severe illness often associated with marked pyrexia, and rapid loss in weight ; and frequently preceded, accompanied or followed by such gastro-intestinal disorder as diarrhœa, vomiting, dehydration and ketosis. Often there is little to indicate the renal tract disorder, such conditions as meningism (especially seen in cases with very high temperature), twitchings and convulsions, and a bulging fontanelle attracting the clinician's attention to the nervous system, but in such cases the cerebro-spinal fluid is normal although its volume is increased. The pyuria in some instances would seem to appear intercurrently or to follow definite disease elsewhere, e.g., otitis media, bronchiolitis, gastro-enteritis ; and the clearing up of the original condition may not be followed by satisfactory clinical improvement. Sometimes abdominal distension and tenderness or definite loin pain may be detected. Vulval, scrotal or gluteal excoriation may be seen. In infancy therefore the examination of the urine may lead at once to a satisfactory diagnosis. In the earliest stages of some very acute cases the evidence of renal tract infection may be little but in a few days frank pyuria and bacilluria appear. Possibly this latter type of case is due to an actual blood-stream infection with the organism which soon becomes localized in the renal tract.

In the older child the symptomatology is more often directly referable to the urinary system, the complaint varying from enuresis to a severe general febrile disturbance with loin pain and tenderness, frequency of micturition, dysuria and opalescent hyperacid urine. In the charts the symptoms are recorded to illustrate the great variability in the clinical picture.

In the whole series of 117 patients the usual duration in hospital was two to four weeks, most cases clearing up quickly under medical treatment. Nine patients died and in each instance (as will be discussed later in greater detail) a more serious disease process was detected, seven showing suppurative pyelonephritis (one case complicated by thrombosis of the left renal vein), one infection of a congenital hydronephrosis and one pneumococcal meningitis. It is significant that eight of the fatal cases were under the age of one year, the youngest infant being only five weeks old. Even so, the mortality rate is low since forty-seven of the cases under treatment were less than two years of age and in the group of seventy cases over two years of age only one died, from suppurative pyelonephritis. Here therefore there is evidence that acute coliform infection may have more serious consequences in the infant.

An outline of the treatment afforded the cases while in hospital has been given by my senior colleague, Dr. K. D. Wilkinson[1], and I shall not here further elaborate this. Certain points must be carefully considered, however, if adequate response to treatment is not observed. Persistent pyuria occurring in some of the cases in this series has been due to (a) suppurative pyelonephritis, (b) infection associated with a congenital malformation in the urinary tract, (c) calculus formation, or (d) residual infection of the posterior urethra or the base of the bladder ; and one or more of these conditions may co-exist. A more detailed study and consideration of these resistant cases is given later.

The acute case.—Is there any evidence of immediate or remote renal damage in the patient who responds quickly to treatment? In only one or two cases has any visible œdema been seen and although in some of the very young children occasional convulsions and twitchings have been seen these latter signs have usually been associated with high temperature and meningism and therefore of doubtful significance as regards uræmia. The urinary findings would not lead one to suspect true nephritis—the albumin content is usually small, casts are nearly always absent although a few red blood cells may appear, and polymorphonuclear leucocytes are in abundance together with the infecting coliform bacilli. The volume of the urine may be normal or diminished in high pyrexia. No significant elevation of the blood pressure has been found. An examination of the blood has been made in some of the patients at intervals throughout the illness and the following two cases illustrate the usual results.

TABLE 1.

SHOWING BLOOD-UREA FIGURES IN ACUTE AND CURED STAGES OF CASES OF ACUTE PYELITIS.

Case No.	Acute stage				Cured stage	
	Urine			Blood urea	Blood urea	Urine
	alb.	pus	casts	mgrm. %	mgrm. %	
1	Present	Present	Absent	41·0	—	Normal
2	,,	,,	,,	27·0	—	,,
3	,,	,,	,,	33·0	32·0	,,
4	,,	,,	,,	72·0	33·0	,,
5	,,	,,	,,	31·0	—	,,
6	,,	,,	,,	38·0	—	,,
7	,,	,,	Present	38·0	—	,,
8	,,	,,	Absent	72·0	26·0	,,
9	,,	,,	,,	42·0	35·0	,,
10	,,	,,	,,	51·0	27·0	,,
11	,,	,,	,,	42·0	21·0	,,
12	,,	,,	,,	21·0	—	,,
13	,,	,,	,,	70·0	30·0	,,
14	,,	,,	,,	75·0	35·0	,,

Case 13.—G. S., girl, aged 11 years. Admitted June 20th, 1930. She had had pain in the back for 8 days, with high fever, frequency of micturition and tenderness in the loins. Diagnosis: acute pyelitis. Treatment by alkalis throughout illness.

On admission: urine acid, albumin +, pus cells +++, B. coli ++, no blood, no casts. Blood urea, 70 mgrm. per cent.

Five days later the condition of the urine was unaltered, and the blood urea was 69 mgrm. per cent. By July 2nd the urine was alkaline, and showed a trace of albumin but no pus: B. coli were still present. The blood urea had fallen to 51 mgrm. per cent. The blood pressure was 95/70. On July 9th the urine was normal, and the blood urea 41 mgrm. per cent. On July 17th the urine was normal, the Calvert test 2·7 per cent. and urea 0·8 per cent. The blood urea was 30 mgrm. per cent. Treatment was abandoned. Recovered.

Case 14.—A. R., girl, aged 1½ years. She had been ill for a few days, with vomiting, drowsiness and high fever (104°). Diagnosis: acute pyelitis. Treatment throughout by alkalies and caprokol.

On admission (June 26th, 1930) the urine was acid and showed much pus and albumin, and was heavily infected with B. coli. No casts or blood present. The blood urea was 74·5 mgrm. per cent. By July 19th the urine was neutral and still showed a little pus with a trace of albumin. On the 28th the urine was normal, and the blood urea 35 mgrm. per cent. Recovered.

The blood urea is seen to be raised soon after the onset of the disease and this nitrogen retention indicates that there is some temporary renal impairment. No casts were found in the urine of either of these two cases and a few cases which have shown occasional casts, no higher, and often lower blood-urea figures have been obtained. It must be admitted, therefore, that some renal damage may occur even in the absence of casts, but this is only temporary and rapidly disappears as the pyuria clears. Table 1 shows a series of cases in which the blood urea was determined in the acute and in the cured stages of the illness.

In each instance the general clinical condition, the urinary and the blood findings indicate a total cessation of the morbid processes in the renal tract and complete recovery can be confidently anticipated. One case of acute pyelitis, two weeks after complete recovery from this disease, died from other causes. A careful examination of the kidneys, ureters and bladder showed a perfectly normal appearance.

Fatal cases.—The acute cases which did not respond to treatment and which ended fatally after a few weeks of illness were examined in detail and in each instance very severe renal disease was found. In most instances suppuration in the kidney substance with considerable destruction of tissue was present or the initial condition was congenital hydro-nephrosis with atrophy of the renal cortex and acute suppuration added.

Pathological reports of fatal cases.

Case 15.—A. R., aged 8 months, female. Had pyuria since aged 10 weeks. Urine contained albumin, pus and B. coli but no blood or casts.

Both kidneys enlarged with numerous irregular swellings on the surface. Each showed many small suppurative foci in the medulla and cortex and a large amount of purulent exudate in the pelvis. The mucosa of the whole urinary tract was congested. Microscopically an intense degree of acute inflammatory cellular infiltration was seen throughout the kidney tissue with abscess formation. The collecting tubules were packed with pus cells and similarly the pelvic mucosa. There is a remarkable absence of change in the glomeruli and excreting tubule epithelium.

Case 16.—B. C., aged 1 year and 4 months, female. Ill 3 weeks. Urine showed albumin, pus, and B. coli.

The kidneys showed thickening and purulent inflammation of the pelves, and many foci of acute inflammatory necrosis and early suppuration in the renal substance.

Case 17.—E. B., aged 3 months, female. Ill 10 days. Albumin, pus, and B. coli present in urine.

The kidneys were enlarged, softened and the pelvic mucosa thickened. Microscopically a considerable degree of hyperæmia and œdema of the pelvic mucosa with frankly suppurative process in the collecting tubules, many of which appear to be blocked up with the exudate, the secreting epithelium and glomeruli showing only slight changes.

Case 18.—B. B., aged 10 months. Ill 5 weeks. Urine showed albumin, pus and B. coli.

The left kidney was twice the normal size, deep red colour with thrombosis of the renal vein. Both renal pelves thickened, dilated and purulent.

Case 19.—B. S., aged 2 months, male. Ill 8 weeks. Albumin, pus and B. coli present in urine. Each kidney enlarged and extremely dilated pelves and narrowed cortex with gross suppuration therein. Ureters also show irregular dilatation. Bladder normal.

These notes concerning fatal acute cases indicate the severity and nature of the lesions found therein. A suppurative process extending into the renal substance renders the prognosis bad, but the only significant differential clinical features indicating this extension of the disease are diminished excretion of urine, persistence of the pyuria, and in some cases a continued severe febrile disturbance with progressive physical deterioration.

End results in fifty-six non-fatal cases.

In order to determine the ultimate conditions present in children who have been under observation and treatment for pyuria, fifty-six patients have been carefully re-examined, especially concerning the general physical progress, the state of the renal tract, the recurrence or persistence of infective pyuria and the cardio-vascular condition. In many instances two or three years had elapsed between the first record and the recent record.

Recovered cases.—Forty-nine of these children were remarkably well when re-examined two or more years after treatment for clinically acute pyelitis. The very satisfactory general impression obtained when examining these children is confirmed by careful investigation in each individual case and in no instance could any physical or mental retardation be detected. The urine, renal function and blood urea is normal in each child. This is confirmatory of the hopeful conditions noted above, when it was shown that in all cases in which the pyuria rapidly cleared, any initial renal impairment was corrected and no later effects on the kidney tissue was demonstrable. In response to enquiries it was found that no child (among the whole series originally treated) had died from renal disease, although four were dead of diphtheria and pneumonia.

Persistent cases.—In the fifty-six children re-examined, persistent pyuria was detected in seven instances whose clinical details are given below. Consideration of each case reveals an interesting reason for the chronicity of the infection.

Case 20.—J. Y., male, aged 7½ years. General condition good. No cardio-vascular changes. No retinal signs. B.P. 100/80. No bone changes. Blood urea 24·8. Has had heavy pyuria with bacillus coli for several years with practically no symptoms. Has been under careful medical control at home.

Intravenous urography shows large dilated kidney pelves, most probably infected congential hydronephrosis (bilateral). There is nothing to indicate bladder disease.

Case 21.—I. G., female, aged 6½ years. General condition good. No cardio-vascular changes. No abnormal retinal signs. B.P. 110/90. Blood urea 30·0 Only symptom is occasional dysuria. Has had intermittent medical treatment. Urine always shows a moderate amount of pus and numerous bacillus coli.

Intravenous urography shows a marked deformity of the right kidney pelvis. Cystoscopy shows a little congestion of the bladder mucosa.

Case 22.—E. S., female, aged 2½ years. General condition good. No signs or symptoms but urine constantly shows large amounts of pus and bacillus coli. Blood urea 45·0. No renal swellings palpable and cystoscopy shows a normal bladder. No urographic examination was possible but almost certainly a congenital defect is present in one or both kidneys, allowing persistence of the infection.

Case 23.—L. W., female, aged 14 years. General condition poor. Anæmia and sallow skin. In 1927 a right pyelogram showed a large dilated right renal pelvis; the bladder was normal. The urine was highly purulent and infected with bacillus coli. Right nephrectomy was performed and the excised kidney showed a very large dilated infected pelvis with atrophy of the renal substance. In 1930 the pyuria and bacilluria are still heavy and there are pain and tenderness and a palpable renal swelling in the left loin. The bladder is normal. Blood urea 56·0. B.P. 110/85. Headaches. Retinæ normal. This child most probably had bilateral congenital renal malformations which became infected with bacillus coli which persisted. A right pyonephrosis was demonstrated in 1927 and excised and in 1930 a similar condition is detectable in the left.

Case 24.—H. M., female, aged 7½ years. General condition poor; small pale child. In 1928 heavy pyuria detected. Bladder normal. Pyelography revealed a large dilated right kidney and ureter with purulent exudate escaping into the bladder. Medicinal treatment and repeated lavage of the diseased ureter and kidney with 5 per cent. collargol failed to clear up the bacillus coli infection. In 1930 the health was poor and the pyuria still marked.

Case 25.—A. A., female, aged 7¾ years. Good general condition. Blood urea 39·0. B.P. 110/90. Pyuria known to exist since 1929.

Intravenous urogram shows a dilatation of the left renal pelvis and a small calculus at the pelvi-ureteral junction.

Case 26.—J. E., female, aged 8 years. General condition very poor. Blood urea 78·0. B.P. 130/95. Polyuria. Specific gravity of urine 1005. Heavy pyuria has persisted for at least three years although practically no urinary symptoms are present. In 1928 the kidneys were examined at operation and the right renal pelvis was found to be markedly dilated, without ureteral dilatation. Also the left kidney was similarly affected but to a lesser degree. This child has therefore chronic infection of bilateral congenital hydronephrosis. There is evidence of advancing renal insufficiency owing to gradual destruction of kidney tissue.

The outstanding point in each case is the presence of some anatomical defect in the renal tract, and this is almost certainly the reason why the infection persists. One girl showed an occasional simple bacilluria and the urethral examination revealed an inflamed mucosa, the renal tract being normal otherwise.

For comparison with the above cases the following are instructive.

Case 27.—D.T., female, aged 16. In 1926 this girl had frequency of micturition, with pain in the left iliac fossa, dysuria and heavy pyuria. This persisted for three years and in 1929 the left kidney and ureter were dissected out and showed a bacillus coli infection of a congenital dilatation of kidney pelvis and ureter as far as the bladder. The right kidney and ureter and the bladder were anatomically normal. The pyuria rapidly cleared and the child's present condition is excellent; weighs 7 stones, blood urea normal and no urinary disorder.

Case 28.—C. T., male, aged 13 years. In 1926 a history of occasional pain in the left loin, vomiting, pyrexia was obtained. The boy appeared ill, was pale and had furred tongue. Physical examination showed a tender soft palpable renal swelling on the left side. Urine acid, albumin present, large amount of pus and bacillus coli.

Operation was performed by Mr. B. Goodwin. The capsule of the left kidney stripped away and a large infected hydronephrotic kidney removed. The ureter below the pelvi-ureteral junction appeared normal and the right renal tract was normal. Within a week the urine was perfectly clear and rapid general improvement had taken place.

Examination of the excised kidney showed a very dilated renal pelvis and an atrophied renal cortex. There was no apparent organic ureteral stricture and no calculi were present. Microscopically a simple pyogenic infection was demonstrated.

In 1930 this boy was re-examined. His general condition is excellent, the cardio-vascular system and renal function is normal, his urine quite clear and sterile and the operation scar perfectly healed.

Sufficient instances of chronic pyuria in children have now been observed to obtain information concerning the progression of the disease. The con-

dition may be detected at the onset, in which case the clinical picture in no way differs from ordinary acute pyelitis. In many cases, however, the disease has been established a variable period of time when first recognized. There may be no symptoms but in most cases one or more complaints are made such as intermittent loin or ureteric pain, enuresis, polyuria or febrile attacks. Many cases, however, remain afebrile for long periods. The pyuria will be detected in some instances on a routine examination of the urine. The frequent absence

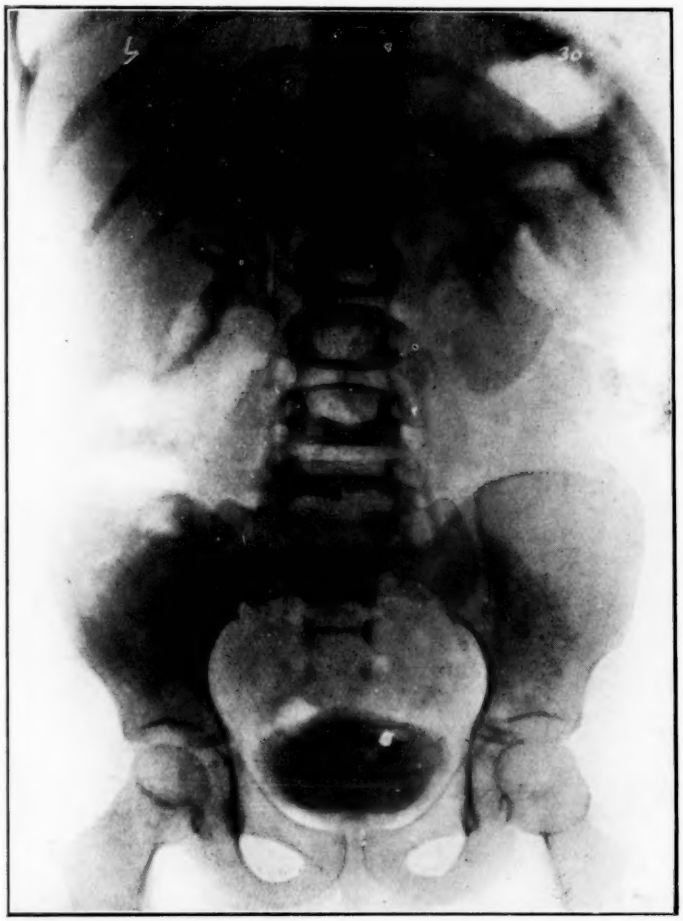

FIG. 1. Case G. B., female aged 6 years. Normal child. Urogram showing normal urinary tract. (¼ hour).

of any general disturbance perhaps for some years is rather remarkable. The benign nature of the general effect is more evident in the cases where the pyuria is due to unilateral renal and ureteric disease, e.g., Cases 20 and 21 above; and the physical effects of the chronic infection are more marked in cases showing bilateral renal tract infection, e.g., Cases 23 and 26. The cases of unilateral infection may undoubtedly continue for many years and the renal enlargement reach a considerable size—no doubt many of the cases of B. coli pyonephorsis and pyo-ureter detected in young adults have arisen in childhood, the chronic

infection arising in a congenital malformation in the upper urinary tract. Provided no acute spread of the suppurative process into the renal substance or sudden dispersion of the infection throughout the renal system takes place, no untoward symptoms occur. If, on the other hand, either through intercurrent illness or otherwise, acute pyelonephritis with intra-renal suppuration supervenes, rapid progress of the disease appears and death from uræmia and toxæmia is usual. When one kidney is normal, anatomically and otherwise,

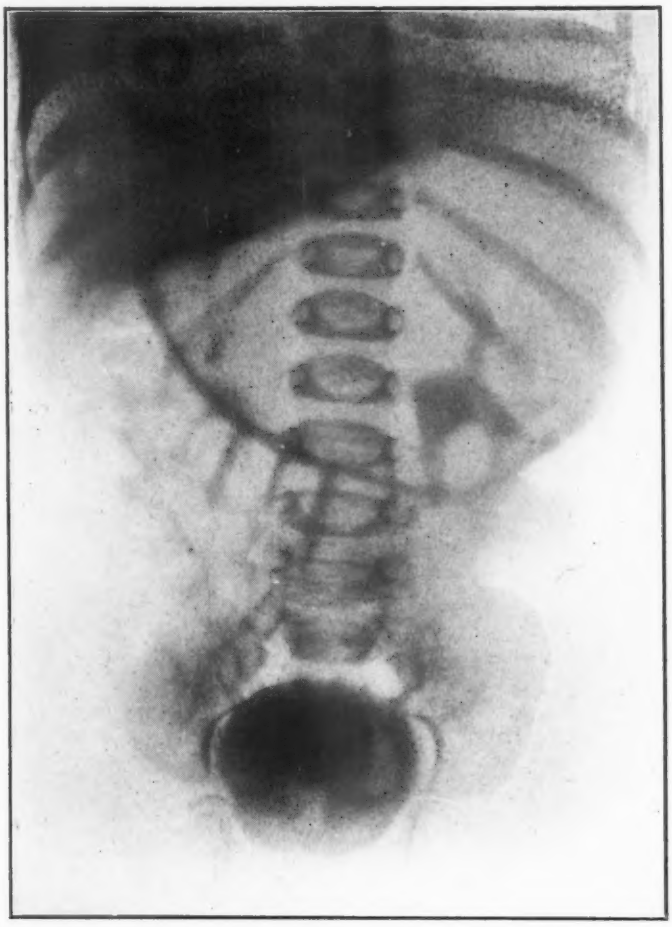

FIG. 2. Case D. C., male aged 6 months. Chronic pyuria. Intravenous urogram showing dilated left renal pelvis. ($\frac{3}{4}$ hour).

considerable hyperplasia can occur to compensate for the gradual destruction of its fellow and consequently renal insufficiency remains absent. On the contrary, where both kidneys are diseased, a slow progressive deterioration is evident and gradually nitrogen retention occurs, e.g., in Cases 23, 26 and 22 where the blood urea has reached 56, 78 and 45 mgrm. per cent respectively. Cardio-vascular changes may appear but are never prominent even in the advanced cases and retinal degeneration is not seen. In the final stages,

which may be several years after the onset of the chronic infection, uræmic manifestations appear and death supervenes rapidly. After death extraordinary deformities in the renal tract are often found, with greatly dilated renal pelves showing gross suppuration and a mere shell of renal secretory tissue left. A remarkable feature in the disease is the postponement of any serious renal failure until so little kidney tissue remains. In certain respects the clinical course strongly resembles that of true congenital cystic disease

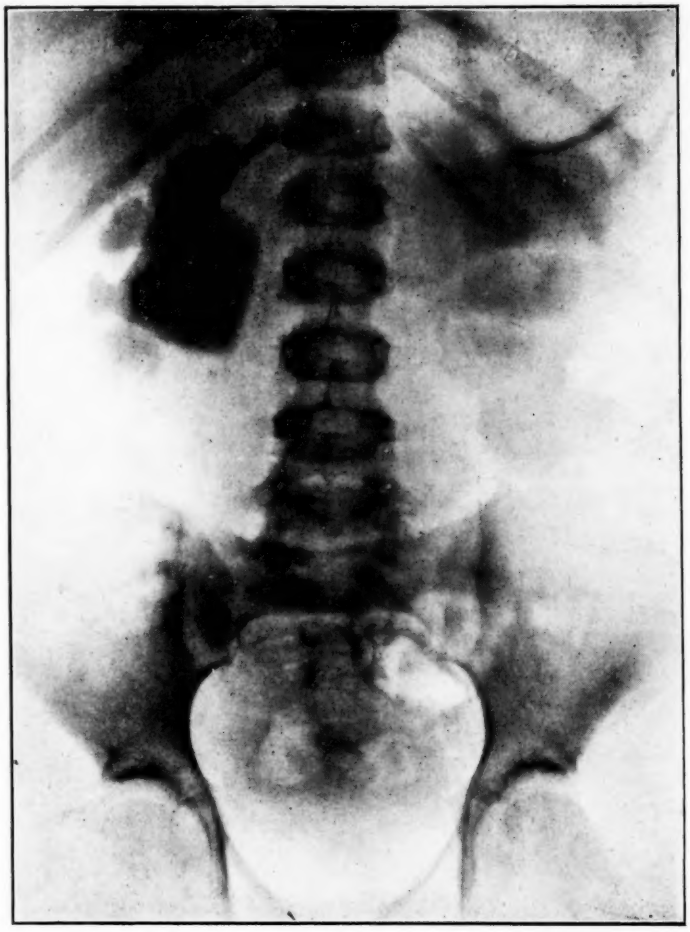

FIG. 3. Case J. Y., male aged 4¼ years. Chronic pyuria. Urogram showing dilatation of the renal pelves. Double pyonephrosis. (2¼ hours.)

of the kidneys, another condition in which symptoms are often absent until an extraordinarily small amount of functionable kidney tissue is left, and where cardio-vascular and retinal changes are minimal and uræmia appears rapidly as a terminal event.

The complete investigation of the patient suffering from chronic pyuria is obviously of great importance in order to determine accurately the reason for persistence of the disease. No case should be allowed to drift along in the

hope of improvement by ordinary medicinal means. No degree of alkalinization of the urine or the use of urinary antiseptics is likely to be of any curative value in an infection associated with congenital deformity of the urinary tract. The recognition of this fact is highly important. Congenital malformations occurring in the kidneys and ureter are no doubt of greater frequency than is generally believed. In the course of a hundred consecutive necropsies in children congenital hydronephrosis of variable degree with or without hydro-

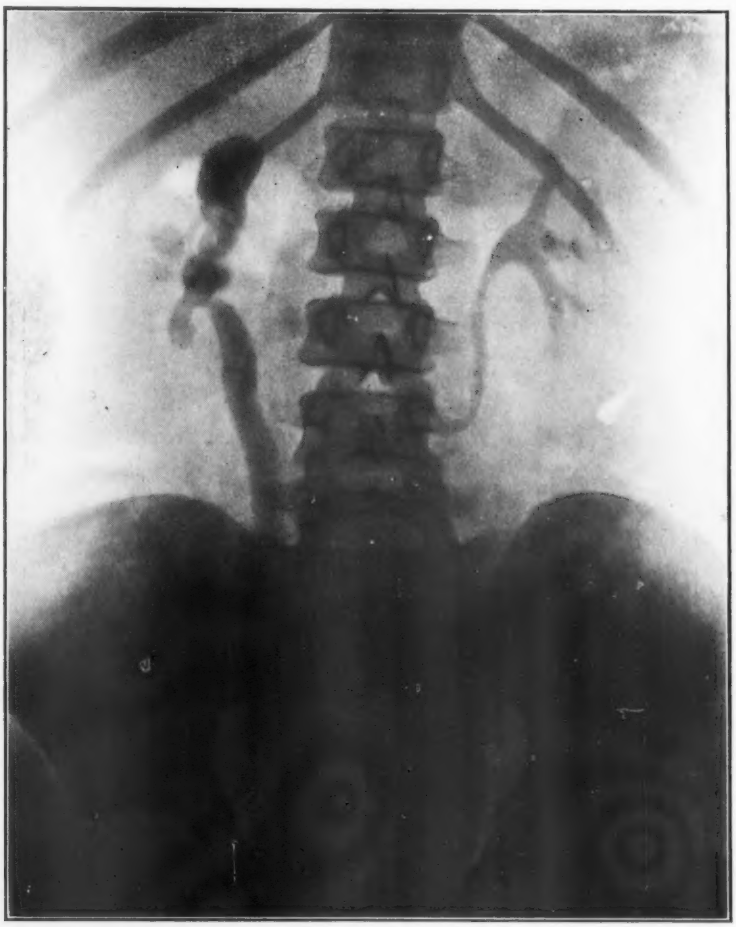

FIG. 4. Case L. L., female aged 9 years. Chronic pyuria. Intravenous urogram showing disease in the right renal tract and a calculus in the right renal pelvis.

ureter, unilateral or bilateral, was found in five or six cases. In most instances no obstructive factor can be found to account for the dilatations and deformities, although in some instances an obvious narrowing in a part of the ureter is detected. Hurst[6] has suggested that such uretero-pelvic dilatation may arise through achalasia of the uretero-vesical sphincter. It is very probable that great interference with the normal pelvi-ureteral peristaltic action takes place when the anatomical outline is distorted and thus stasis is likely to occur which

is doubtless an important factor in preventing adequate power to eliminate infective material. It is therefore necessary to examine each patient for urinary tract malformations.

There are certain difficulties in applying the usual surgical procedures in investigating children. Cystoscopy usually presents no difficulties, but pyelography by ureteral catheterization may be extremely difficult or impossible

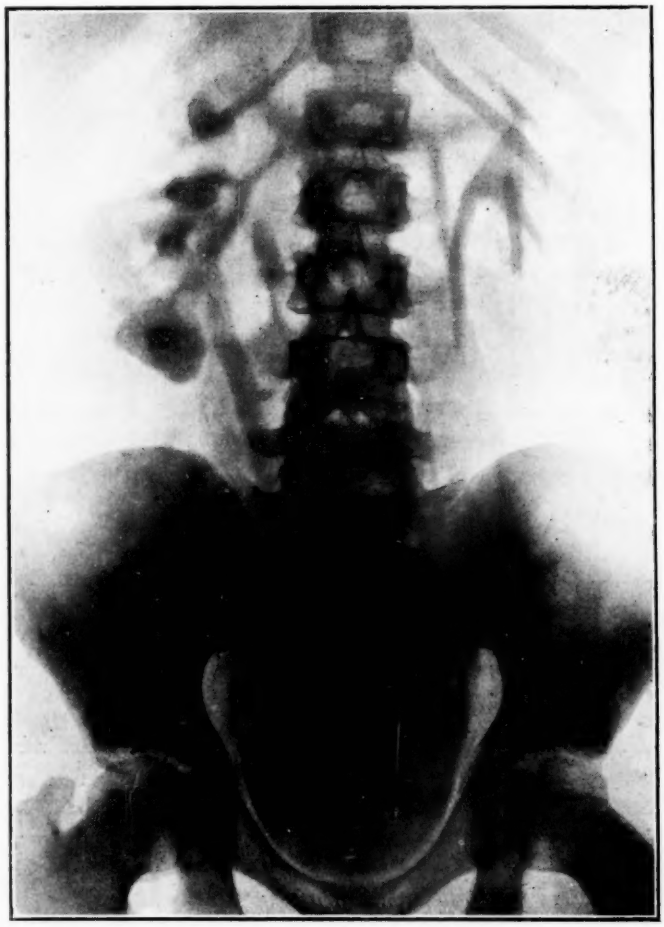

FIG. 5. Case L. L., female aged 9 years. Chronic pyuria. Intravenous urogram showing disease in the right upper renal tract. 2nd. test after operation for removal of calculus.

to carry out, if any serious degree of ureteral narrowing is present. The cystogram is useful occasionally, and ureteral reflux is shown in some abnormal conditions of the tract, but distortions and dilatations of the upper parts of the ureter and renal pelves are not shown.

By the use of intravenous injection of uroselectan (a pyridine compound containing 40 per cent. of organically combined iodine) followed by radiography, a very useful method of investigating the anatomy of the renal tract in

children is now available. This substance which is opaque to X-rays, and practically non-toxic, is rapidly eliminated by the kidneys if advanced renal impairment is not present. Normally it appears in the bladder in about ten minutes after the intravenous injection, and very soon the renal pelves, ureters and bladder become distinctly outlined.

TABLE 2.

CURED CASES INVESTIGATED BY UROGRAPHY.

Date	Case No.	Age	Sex	History	Blood	Calvert test	Urogram	Remarks
1930	A. D.	10	F	Acute pyelitis with pyuria 1927. Cured after a few weeks.	Urea 36 U.Ac. 2·7	A 290 c.cm. 4·4% B 220 c.cm. 1·5%	No calculus. Excretion rate normal. Tract normal.	No renal tract defects. Pyelitis cured.
1930	H. P.	9	F	Pyelitis 1925. Pyuria cleared in a few weeks.	Urea 35 U.Ac. 2·7	A 270 c.cm. 4·6% B 375 c.cm. 1·2%	Excretion normal. Tract normal.	ditto
1930	L. M.	14½	F	Pyelitis 1927. Pyuria cleared. Bacilluria.	Urea 30	—	Excretion and tract normal. Cystoscopy shows a few inflamed urethral glands.	ditto
1930	G. B.	6	M	No disease.	Urea 30	—	Excretion and tract normal.	
1930	D. T.	9	F	Acute pyelitis. Pyuria clear in 2 weeks.	Urea 39	A 380 c.cm. 3·2% B 480 c.cm. 0·9%	Excretion and tract normal.	ditto
1930	D. L.	9	F	Acute pyelitis, cured.	Urea 38	A 235 c.cm. 4·2% B 620 c.cm. 0·6%	Excretion and tract normal.	ditto
1930	13	11	F	Acute pyelitis 1929. Cured in 2 weeks.	Urea 31	A 540 c.cm. 2·7% B 330 c.cm. 0·8%	Excretion and tract normal.	ditto
1930	J. R.	8	F	Acute pyuria. Cured in 1 week.	Normal.	A 325 c.cm. 3·2% B 660 c.cm. 0·6%	Excretion and tract normal.	ditto
1930	J. E. P.	6½	F	Acute pyuria. Cleared in 2 weeks.	Normal.	—	Excretion and tract normal.	ditto

In order to demonstrate the absence of any defective mechanism or deformity in the renal tract in cases of acute pyuria which rapidly clears up after ordinary medicinal treatment, a series were examined by the urographic method and the details are given in Table 2.

A number of children with chronic pyuria have been similarly examined by intravenous urography and Table 3 shows the results. In each case a

deformity in the renal tract is present. In two patients Cases 25 and L. L. calculus formation had occurred.

Treatment in chronic pyuria should be carried out with careful consideration of all the points in the case. Detection of foci of infection elsewhere and

TABLE 3.

CHRONIC PYURIA CASES INVESTIGATED BY UROGRAPHY.

Date	Case No.	Age	Sex	History	Blood urea	Calvert test	Urogram	Remarks
1930	25	7¾	F	Pyuria detected 1929. Persistent after medical treatment, etc.	39·0	A 310 c.cm. 4·8% B 370 c.cm. 0·9%	Left kidney shows dilatation of the renal pelvis with a small calculus. Right kidney and ureter normal. Excretion rate normal.	Persistent pyuria associated with defect in the left renal tract.
1930	20	4¼	M	Pyuria first detected in 1927—has been persistent ever since.	36·0	A 325 c.cm. 1·8% B 110 c.cm. 2·0%	Both kidneys show extensive deformity. No calculus.	Persistent pyuria associated with bilateral renal tract deformity.
1930	P. W.	1½	F	Pyuria since 1929. No response to treatment.	43·0		Renal shadows both large and irregular. No calculus.	ditto
1930	J. L.	3	F	Pyuria 6 months. No response to treatment.			Right side shows a dilated kidney and dilated ureter. Left side normal.	Persistent pyuria associated with right renal tract deformity.
1930	D. C.	½	M	Pyuria detected age 2 months — persistent.			Very dilated left kidney pelvis. Right appears normal.	Chronic pyuria and left renal deformity in an infant.
1930	21	6	F	Pyuria detected 1927.	30·0	A 325 c.cm. 3·9%	Right kidney shows a marked pelvic deformity. Ureter and left side normal.	Chronic pyuria with right renal deformity.
1930	L. L.	9	F	Pyuria with occasional hæmaturia at least 18 months.	37·0	A 3·9% B 0·5%	Right hydronephrosis and hydro-ureter. A calculus present. Left tract normal.	Chronic pyuria with right renal tract deformity and calculus.

their eradication is necessary. Most children will show the general effects of chronic sepsis and the physical condition should be improved before any urographic or surgical investigation is made. A full investigation of the renal function is best carried out in children by the urea-concentration method

of Calvert and the blood-urea estimation. Radiographic investigation for calculus formation and intravenous urography for determining the anatomical outline of the urinary tract is required. Sometimes a cystoscopic examination of the bladder is of use, a diverticulum may be detected or chronic secondary cystitis seen.

Direct treatment of a chronic infection of the renal pelvis and ureter has been carried out in some cases by ureteral catheterization and renal lavage with colloidal silver preparations, but very little improvement has followed. Irrigation of the bladder with antiseptic fluid, or the daily injection of small amounts of weak silver nitrate solution, has not met with any marked success, as might be expected where purulent urine is continually entering the bladder.

Alkalies, hexamine, hexyl-resorcinol, 'pyridium,' vaccines and bacteriophage have all proved of very little permanent value in chronic pyuria associated with renal tract deformity.

Reference to Cases 27 and 28 detailed above illustrates the great benefit obtained and complete cure of the pyuria following removal of the diseased kidney. In each child complete recovery has occurred, the urine and renal function are now normal, and the physical condition excellent. It appears, therefore, that the only treatment of permanent value is surgical removal of the diseased part of the renal tract. In patients where the condition is unilateral this can be carried out very satisfactorily, but obviously where bilateral disease exists no such procedure is possible. In the latter cases general medical supervision should be made to preserve the physical condition and general resistance as long as possible, and so delay the occurrence of uræmic toxæmia. Under such conditions the patient may survive for many years, in fact as long as the diminishing functionating kidney tissue lasts, provided that no rapid intercurrent infection of the renal parenchyma takes place.

Discussion.

Our studies in acute pyuria have yielded considerable information concerning the clinical progress, certain prognostic features and the remote conditions following acute infections of the renal tract. Enquiry has shown that there is no general physical or renal impairment in any of the patients who rapidly responded to treatment, and complete cure is established in all the patients re-examined from two to five years after the acute illness. This group of cases includes all those who have suffered from acute pyelitis, usually due to B. coli infection.

Broadly speaking, the older the child the less is the probability of any serious involvement of the renal parenchyma. In infants and young children, however, a general spread of the purulent process into the kidney substance may take place and suppurative pyelo-nephritis supervene, which almost certainly renders the condition an extremely grave one. In all the fatal cases of acute renal tract infection post-mortem examination has shown this change.

Cases of chronic pyuria, that is where purulent urine occurs over a period

of months or years, have received special attention, and various methods of investigation have been utilized in order to find the usual reasons for this perpetuation of the infection in the urinary tract. In the first place the remarkably good general condition of many children with chronic pyuria indicates that, in most instances, no serious renal dysfunction exists. Therefore it is highly probable that the infective condition does not directly involve the renal parenchyma. In fact the length of life under these conditions depends upon the absence of spread to the renal secretory tissues. On the contrary, as shown by the clinical records and necropsy examinations, an acute extension of the suppuration to the kidney tissues exists in the fatal cases.

In nearly all cases of chronic suppuration in the renal tract the primary focus of the disease lies in the supra-vesical portion, in the ureter and renal pelvis. Very rarely the chronic infection is due to some abnormality in the bladder such as a congenital diverticulum or urethral mucosal valves producing deficient bladder action, or it is associated with disease in the nervous system. Addison[2] has outlined the clinical features and methods of treatment in cases of congenital valvular urethral obstruction with vesical and ureteral dilatation.

The embryological development and growth of the bladder, ureters and renal pelvis from the cloaca and the ultimate union with the metanephric tissues is a complex process, and it is not surprising that developmental abnormalities should appear in the tract. Congenital polycystic disease is due to intra-renal malformation usually explained as a failure of union between the collecting tubules and secreting tubules. We are concerned here with defective malformations at a lower level. Hyman[3] notes that the incidence of malformations in the urinary organs is 2·3 per cent. of all post-mortem examinations in children, and the greater number occur in the upper part of the tract leading to hydronephrosis and later pyonephrosis. Improper drainage, resulting in stasis and chronic infection, usually brings the patient under observation. The sexes are about equally affected and abnormalities in the genitalia are sometimes present also. Congenital hydronephrosis is one of the commonest varieties, Bugbee[4] finding 53 cases in 4,000 necropsies. These conditions often remain unrecognized until of palpable size or infection of the part occurs, the latter sometimes remaining symptomless for many months. Dilatation of one or both ureters, sometimes to an extreme degree and involving the whole length or only a segment of the tube may be present, and often the ureteric orifices are gaping or normal in appearance. The pathogenesis of such conditions has not been satisfactorily explained but possibly failure of important neuromuscular connections is present—in fact it may be somewhat comparable to congenital megacolon. Poynton and Sheldon[5] have given a careful review of some of the clinical and pathological aspects of dilatation of the ureters and bladder and they note the numerous varieties which are seen, some showing definite organic stricture and others not revealing any such cause. It is quite apparent that a great variety of malformations are possible in the renal tract, and many types have been found. In the present discussion the important thing is their realization as a very important factor in chronic urinary infections. Whereas formerly the condition

was often a necropsy finding, instances are now more frequently recognized as a result of special urological studies in the cases. Systematic physical examination may disclose other congenital defects such as epispadias, hypospadias, atresia ani, spina bifida, etc., and sometimes a unilateral genital defect is present on the same side as a unilateral urinary abnormality.

Two instances of unilateral congenital hydronephrosis are shown in the drawings (Figs. 6 and 7) :—

(a) Male, aged 1½ years. Died of acute septic meningitis. Never any urinary symptoms and the urine was normal. The left kidney was found to possess a dilated pelvis without ureteral abnormality or obstruction and the right kidney, ureter and the bladder were quite normal (Fig. 6).

(b) Female, aged 2 years. Died of tuberculous meningitis. Never any urinary symptoms and the urine was normal. The right kidney showed a congenital hydronephrosis and no ureteral disease ; the left kidney, ureter and the bladder were normal (Fig. 7).

The principle diagnostic aid in the recognition of defects in the urinary tract are radiographic. The ordinary cystogram or pyelogram may be used but the use of the intravenous uroselectan method is of special value in children. Uroselectan is a neutral, water-soluble, non-toxic organic compound of iodine and pyridine, opaque to X-rays, and which when injected intravenously in 40 per cent. solution is rapidly excreted by the kidneys, and a radiographic outline of the urinary tract is obtained. Fig. 1 shows the normal picture, the renal pelves, ureters and bladder being shown. Radiographs of patients showing renal tract defects are also shown. In Case L.L. an ordinary radiogram showed a calculus in the right kidney pelvis, but urographic examination revealed advanced hydronephrosis and hydro-ureter without ureteric obstruction, the left side being normal (Fig. 4).

This simple method of demonstrating renal tract defect in chronic pyuria is of considerable value in arriving at a complete diagnosis in these cases.

Conclusions.

1. Clinical studies in a large series of cases of acute pyelitis in children show that although there may be a slight degree of impairment of kidney function in the acute pyrexial stage, there is no permanent or progressive renal damage and complete cure follows medical treatment.
2. Fatal cases of acute purulent renal tract disease in children show suppurative pyelonephritis with considerable destruction of the renal parenchyma.
3. Chronic pyuria is nearly always associated with congenital anatomical defects in the renal tract which impede the normal peristaltic movement and drainage.
4. The use of intravenous uroselectan, enabling urographic examination to show these defects, is of special value in children.
5. The treatment which has proved of permanent value and curative in chronic pyuria associated with renal or ureteral malformation, is excision of the diseased part of the upper renal tract in unilateral cases. In bilateral conditions surgical measures are not possible.

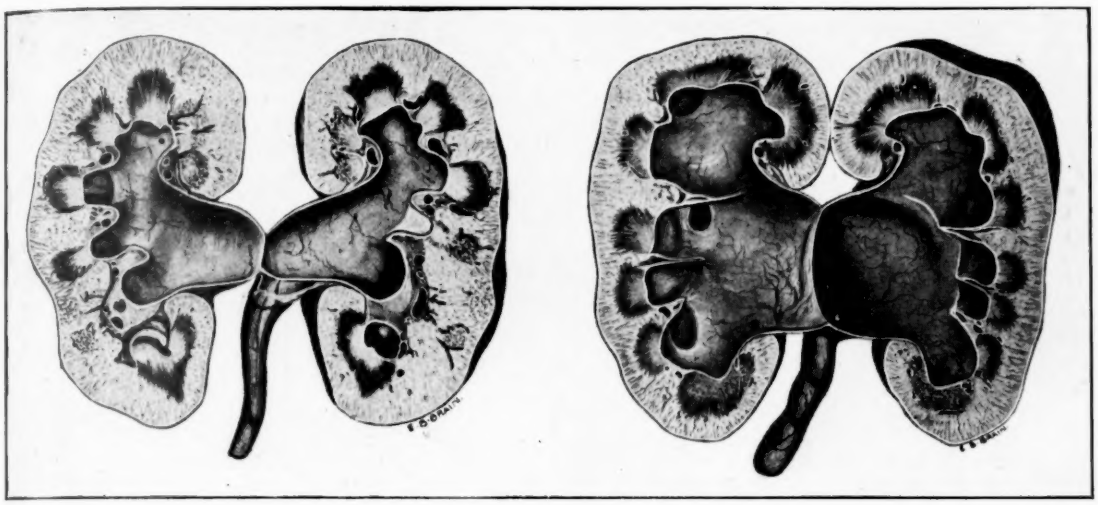

FIG. 6. J. M., male, aged 1½ years. Died of pneumococcal meningitis. Never any urinary symptoms and urine normal. The left kidney found to have dilated pelvis with normal lower urinary tract. Right kidney and ureter normal. Congenital hydronephrosis.

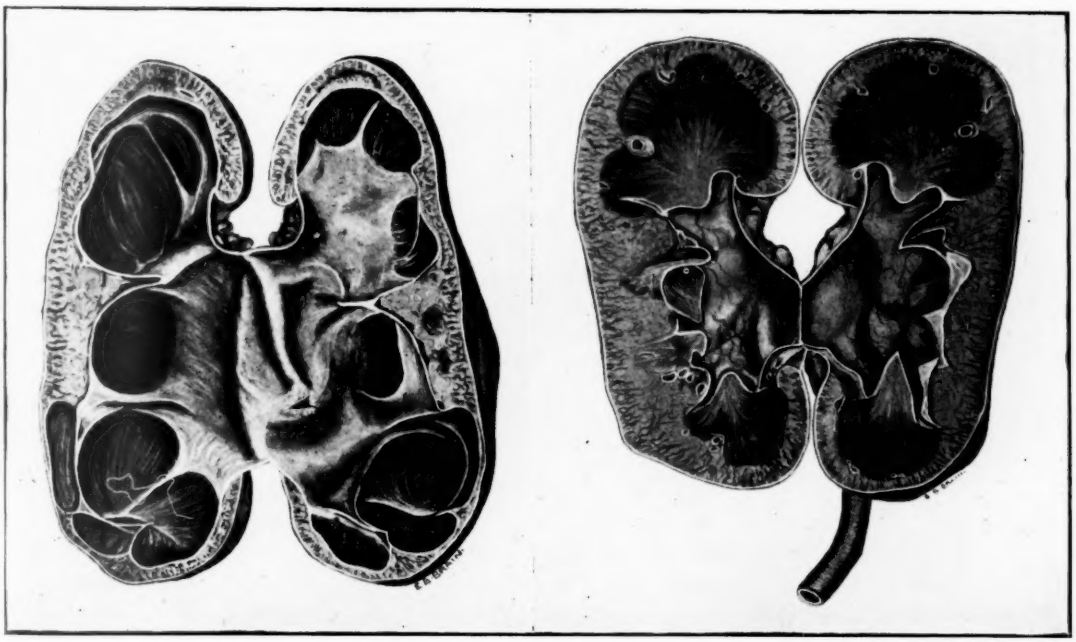

FIG. 7. Joan M., female aged 2 years. Death from tuberculous meningitis. Never any urinary symptoms and urine normal. The right kidney showed a congenital hydronephrosis without any evidence of ureteral obstruction or dilatation. The left kidney and ureter were normal. Bladder and urethra normal.

I am extremely grateful to the physicians and surgeons of the Children's Hospital, to the radiologists, Dr. Teale and Dr. Thorpe, and to the biochemist, Dr. Hickmans, for collaboration in this work.

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DISTRIBUTION OF THE PHOSPHORUS COMPOUNDS AND CALCIUM IN THE BLOOD OF CHILDREN*

BY

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PART I.—NORMAL CHILDREN.

During the past 15 or 20 years our knowledge of the phosphorus content of the human blood has been considerably advanced by the work of several investigators. The inorganic phosphorus fraction, which is only about one-tenth of the total phosphorus content of the whole blood, appears to have claimed the attention of most of the previous workers, and, therefore, abundant data are available from the literature both for health and disease. Because of this, the inorganic phosphorus of the blood has already acquired some definite practical clinical value. The other compounds of phosphorus in the blood have attracted, however, the attention of fewer workers. The results of the present investigations are published in the hope of throwing further light on the distribution of phosphorus in the blood of the child, and especially on the quantitative changes resulting from disease.

Methods.—1. The method used for all the estimations of phosphorus compounds was, with one or two slight modifications, that adopted by Kay and Byrom[1].

2. Determinations of the calcium content of the blood serum were made according to the method described by Kramer and Tisdall[2].

While in studies of this nature it is probably desirable to obtain all the samples of blood in the morning after a whole night's fasting, it proved impracticable in every case to adhere to such a rule. At least 4 hours were allowed to elapse after a meal before the sample of blood was taken for analysis. This interval is probably long enough to exclude any direct influence of the meal on the partition of blood phosphorus. Venous blood was used with a minute quantity of potassium oxalate as anti-coagulant.

As very little is known at present regarding the equilibrium existing between the various forms of the phosphorus in the plasma and in the red blood corpuscles, or the ease with which an exchange may take place between the corpuscles and the plasma, the analytical procedures were commenced immediately the samples of blood were obtained.

Kay and Byrom[1] used the substance 'Heparin' as the anti-coagulant in the samples of blood for the hæmatocrit values, and potassium oxalate in that for the estimations of phosphorus compounds. In this study potassium oxalate was invariably used. It is true that the osmotic pressure of potassium oxalate is relatively high, and, as Rossdale[3] pointed out, the addition of oxalate reduces the corpuscular volume per 100 c.cm. of blood. But, as oxalate is also used in the separation of plasma from the cells for the estimation of the phosphorus compounds, there is

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the advantage of comparing plasma volume and phosphorus content on samples prepared by the same method, whereas Kay and Byrom used ' Heparin ' for the samples of blood used for the hæmatocrit readings and oxalate for those used for the analysis.

Results.—The results of direct analysis of the whole blood and the plasma for the phosphorus compounds, with the calculated results from these for the red blood corpuscles, of 10 normal children are given in Table 1 (pp. 202-3).

Discussion.

Hæmatocrit findings.—The average corpuscular volume of blood in 10 children was found to be 33·15 per cent., the highest being 38·8 per cent., and the lowest 28·7 per cent., of the whole blood. McKellips[4] and his co-workers reported an average of 44·3 per cent. for children, and Kay and Byrom[1] gave an average of 43 per cent. for adults, but the latter noted the same range of fluctuation between the individual cases as reported for the cases of this paper.

Inorganic or free phosphorus.—The average free phosphorus in 10 normal children was found to be 4·15 mgrm. per cent. of the whole blood, 3·93 mgrm. per cent. of the blood plasma, and 4·63 mgrm. per cent. of the red blood corpuscles, showing that the corpuscles are richer in free phosphorus than the plasma. Our average value for the blood agrees with the findings of Hess and Gutman[5], and Riesenfeld and his co-workers[6], while Zucker and Gutman[7], and Anderson[8] reported slightly higher values. On the other hand, Jones and Nye[9] reported an average value of 3·1 mgrm. per cent., Taylor and Miller[10] found no inorganic phosphates present in the serum ; and Buell[11] failed to find inorganic phosphates in the red blood corpuscles both of the dog and the human subject.

Ester phosphorus compounds.—The average ester phosphorus of 10 normal children was 22·4 mgrm. per cent. of the blood, 0·38 mgrm. per cent. of the blood plasma, and 67·25 mgrm. per cent. of the red blood corpuscles. These findings fully confirm the results of other workers that the blood plasma contains only a negligible quantity of the ester phosphorus, and that practically all the ester phosphorus is held by the corpuscles. Kay and Byrom termed the amount of the ester phosphorus per cent. of the red blood corpuscles the ' phosphoric index ' of the blood, and they held that it was very constant in the normal adult. According to their findings, it had practically the same value of 53, rarely varying more than 10 per cent. on each side of the mean. Our results yield the ' phosphoric index ' of 67·25 with a variation of about 20 per cent. in either direction of the mean value. This difference in the ' phosphoric index ' would suggest that the red blood corpuscles of children are richer in the ester phosphorus compounds than those of adults.

Lipin phosphorus compounds.—The average lipin phosphorus was 13·74 mgrm. per cent. of the blood, 9·06 mgrm. per cent. of the blood plasma, and 23·26 mgrm. per cent. of the red blood corpuscles. Jones and Nye found, as calculated from their results given in terms of H_3PO_4, 9·3 mgrm. per cent. for the blood plasma, and 19 mgrm. per cent. for the corpuscles. McKellips and his co-workers reported 17 mgrm. per cent. for the red blood corpuscles

for children. Bloor[1 2], and Kay and Byrom reported 18·7 mgrm. per cent. and 18 mgrm. per cent. for the corpuscles of adults respectively.

It has not been sufficiently emphasized that the lipin phosphorus compounds of the corpuscles in normal children, though nearly three times less in amount than the ester phosphorus, appear equally constant.

Calcium content of the blood serum.—The average calcium content of the blood serum of 9 normal children was found to be 10·73 mgrm. per cent. the highest figure being 11·1, and the lowest 10·08.

There appears to exist no evident relationship in distribution between the calcium of the serum and any phosphorus compound in either whole blood, blood plasma or corpuscles from these results.

Summary.

(1) The blood of normal children is relatively richer in all the phosphorus compounds than that of adults, and the phosphorus compounds in the blood of children tend to show slightly greater variations in distribution than those of adults.

(2) The red blood corpuscles contain more free phosphorus per cent. than the plasma.

(3) The ' phosphoric index ' of the blood shows a tendency to be higher, but slightly less constant, in children than in adults.

(4) The lipin phosphorus of the red blood corpuscles is almost as constant an ingredient as is the ester phosphorus.

(5) The hæmatocrit value of the blood in children is lower than in adults.

(6) The average calcium content of blood serum is 10·73 mgrm. per cent.

PART II—NEPHRITIS.

In all investigations of this nature the initial stumbling block is the clinical classification of the types of nephritis. A simple separation into (a) acute, (b) subacute, and (c) chronic groups has been adopted here. The acute group includes all the cases suffering from the first attack of nephritis from which apparent recovery usually follows within two months. The subacute form comprises all the cases with the primary attack of nephritis of more prolonged duration, in which the disease has lasted for a period of some months. The chronic group consists of all the cases of nephritis in which the attack is either prolonged into years or in which there have been recurrent attacks of the same condition.

As early as 1915 Greenwald[1] showed that in many cases of nephritis the acid-soluble phosphorus of human blood serum was markedly increased, together with great variations in the lipoid phosphorus content. Since then the researches of Marriott and Howland[2], Bloor[3], Epstein and Rothschild[4], Denis and Minot[5], Denis and Hobson[6], Briggs[7], de Wesselow[8], Hiller and his co-workers[9], Daniels[10], and Byrom and Kay[11] have added considerably to the elucidation and interpretation of the changes in the partition of phosphorus compounds of the blood in renal

diseases. Of all the previous workers Byrom and Kay were the first to study the simultaneous behaviour of all the phosphorus compounds of the blood in renal diseases. Further, all the workers studied these changes in the blood of adult patients.

Here an attempt has been made to study the changes in the partition of phosphorus compounds of the blood in 10 nephritic children, 8 of whom were in the acute stage, one in the subacute, and one in the chronic stage. In 5 of the 8 patients, who were suffering from acute nephritis, an endeavour was made to study the behaviour of phosphorus compounds of the blood during the whole course of the disease so that the samples of blood were submitted to complete analysis at different stages of the disease. In the remaining cases the analysis of blood was carried out only on one occasion. The results are given in Table 2 (pp. 202-3).

Discussion.

Inorganic or free phosphorus.—The findings for the free phosphorus of blood in 10 nephritic children correspond to a large extent with those of the other workers. In all the cases there was a tendency for the free phosphorus of blood to rise above the level of normal average during the disease except in Case 2. This child was suffering from acute nephritis with definite symptoms of uræmia, and the free phosphorus never rose above the normal level.

In most of the cases the rise in the free phosphorus and the retention of non-protein nitrogen occurred simultaneously, but this was not invariable as Cases 2 and 3 testify. No satisfactory explanation has been offered for these differences, and, in all probability, more than one factor is responsible.

(1) It might be the result not so much of the variation in the excretion as of the variation in the diet, and in the demand for phosphorus and nitrogen for anabolic purposes.

(2) There might be different mechanisms in the kidney for the excretion of waste products, namely, phosphates and urea, and these mechanisms might be, but need not be, impaired or damaged at the same time.

(3) Non-protein nitrogen retention in the blood might be due to the damage of the kidney, and the rise in free phosphorus of the blood might be due to the impairment of the regulating mechanism for the synthesis of the phosphorus compounds in the blood.

De Wesselow pointed out that the inorganic phosphate retention was apparently more definitely connected with the symptoms of uræmia than was the non-protein nitrogen retention, but neither of our two cases of acute nephritis with symptoms of uræmia lend support to his statement. He also suggested that the phosphoric retention involved certain deleterious results which the findings of our two cases did not support, because both of them exhibited marked symptoms of uræmia before there was any rise in the free phosphorus of blood. Further, Greenwald[12] studied the supposed toxicity of sodium phosphate, and he concluded that there was no evidence of direct toxic action of the phosphorus ions.

It can be readily seen from the Chart I that the rise of free phosphorus of the blood was highest during the acute stage of the disease, and it showed a tendency to taper off gradually as the condition improved. The free

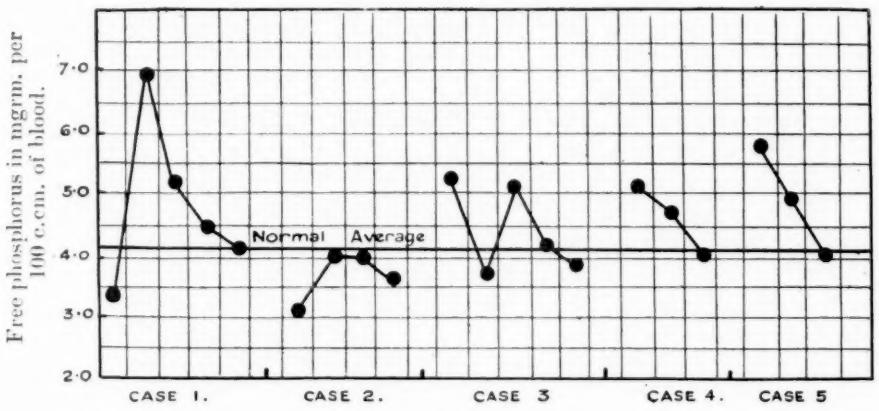
phosphorus curve could be fairly well correlated with the clinical condition of patients, but it takes longer to come down to the normal level than the clinical signs and symptoms, for at the time of discharge from hospital, when the patients were considered completely cured clinically, it was still slightly above the normal level. Later the estimations of the blood were repeated, and the free phosphorus was found within the limits of normality.

In normal blood the free phosphorus was invariably found greater in amount per cent. in the corpuscles than in the blood plasma, but in the blood of nephritic children the free phosphorus was often disturbed, and its concentration was higher in the blood plasma.

Ester phosphorus compounds.—In all the five cases of acute nephritis studied during the whole course of the disease the ester phosphorus content of the whole blood was slightly diminished in amount per cent., which diminution was due not so much to the impoverishment of the red blood

CHART I.

Free phosphorus of blood in cases of nephritis during the disease.



corpuscles, which contain the bulk of the ester phosphorus compounds, as to the relative decrease in the portion of the red blood corpuscles per 100 c.cm. of whole blood.

The ester phosphorus of blood plasma, though normally very small in amount per cent., was, nevertheless, often found greatly increased during the course of disease, in one case reaching a value of 2·17 mgrm. per cent., i.e., more than five times the normal average value. Our findings agreed with those of Byrom and Kay who gave an average value of 0·5 mgrm. of the ester phosphorus per 100 c.cm. of blood plasma.

The average ester phosphorus of the red blood corpuscles, or the so-called phosphoric index of blood, for the 5 cases of acute nephritis was found to be 67·51 mgrm. per cent. which was within the limits of normality. This average figure would tend to negative any suggestion that there was an accumulation of the ester phosphorus content in the corpuscles during the disease; but, on closer examination of the figures, in 4 out of 5 cases the ester phosphorus

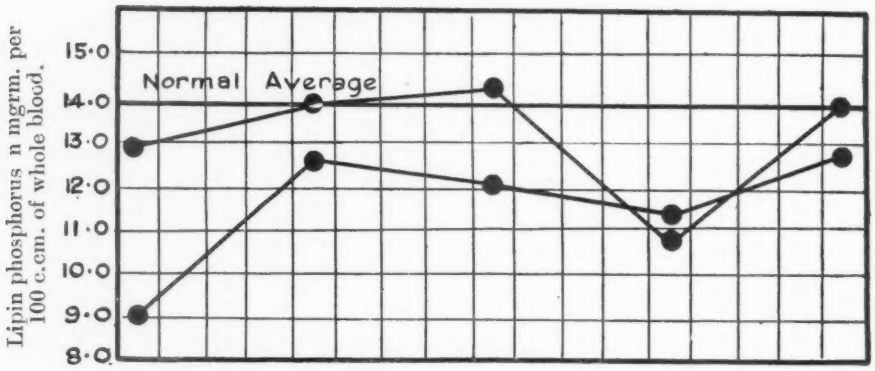
content of the corpuscles showed a tendency to be appreciably increased in amount per cent. at the onset of disease, the actual figures for the 4 cases being 72·7, 90·4, 83·7 and 74·0 mgrm. per cent. respectively.

The findings in the individual cases suggested that the regulating mechanism of the ester phosphorus of red blood corpuscles in nephritis was altered, for, at certain stages of the disease, the corpuscles seemed to be called upon to accommodate a greater amount of the ester phosphorus compounds per cell-unit, while at other stages they were called upon to release these compounds at a quicker rate.

Lipin phosphorus compounds.—The lipin phosphorus compounds of whole blood were found to be relatively slightly diminished in amount per cent. at the commencement of acute nephritis. They showed a tendency to rise appreciably, only to fall again during the course of disease, but they regained the limits of normality at the end of complete recovery. Thus in Case 1 the lipin phosphorus content of blood was 12·82 at the onset of disease, then rose

CHART II.

Lipin phosphorus o the blood during the course of acute nephritis in two patients.



gradually to 14·1 only to fall again to 10·88 mgrm. per cent. during the course of the illness: on complete recovery the lipin phosphorus rose again to 13·8 mgrm. per cent. These changes are well illustrated by Chart II.

The lipin phosphorus content of blood plasma in the individual cases showed a tendency to fluctuate during the acute stage of nephritis, and in 2 out of 5 cases the percentage content was very low. For instance, in Case 1 the percentage content varied from 5·1 to 10·2 mgrm. during the course of the illness.

The lipin phosphorus compounds of the red blood corpuscles showed a very marked tendency to fluctuate in amount per cent. during the illness. Thus in Case 1 the lipin phosphorus content of corpuscles fluctuated between 15·5 and 31·7 mgrm. per cent. at different stages of nephritis.

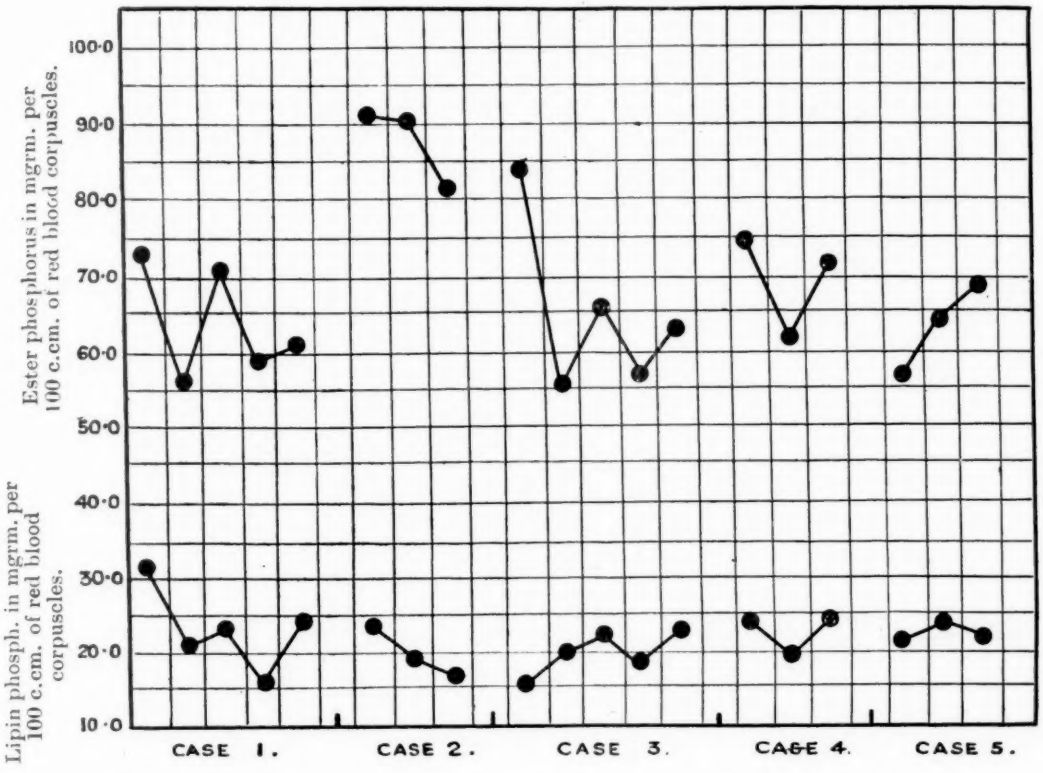
Our results for the lipin phosphorus of blood in acute nephritis fall partially into line with those published by Byrom and Kay, who found that the alcohol-ether soluble phosphorus of the blood was, on the average, diminished slightly

in amount per cent. in acute nephritis, increased slightly in subacute, and almost normal in chronic nephritis. On the other hand, they maintained that, in the majority of cases, the alcohol-ether soluble phosphorus of the blood plasma was above the normal value while that of the corpuscles remained constant or nearly so.

Further, the findings lead to the belief that there was an inter-relation between the lipin and ester phosphorus compounds of the red blood corpuscles. Their percentage increases or decreases tended to run parallel as can be seen from Chart III.

CHART III.

Showing simultaneous rise or fall in the lipin and ester phosphorus of red blood corpuscles in five cases of acute nephritis.



Total phosphorus content.—The average total phosphorus content of the whole blood of 19 estimations in nephritis was found to be 37·75 mgrm. per cent. This amount is 5·8 per cent. below the normal average.

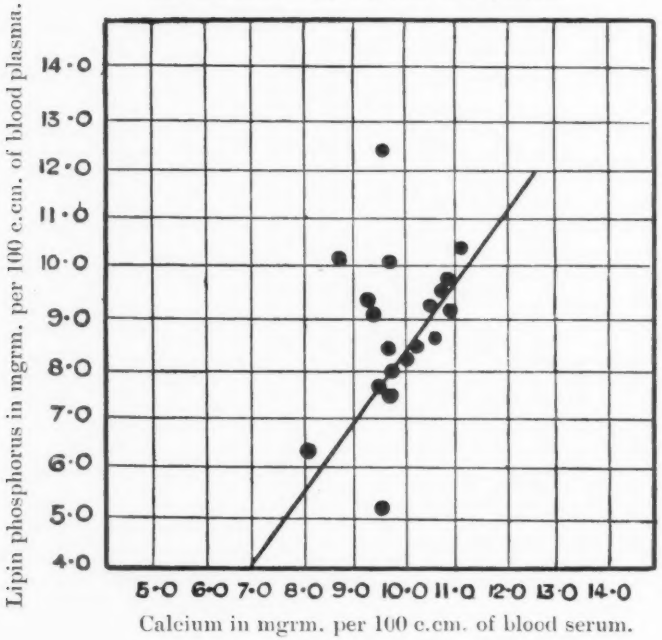
The total phosphorus content of the blood in individual cases studied at different stages of the disease showed a tendency to vary in amount per cent. Thus in Case 1 it varied from 35·12 to 40·5 mgrm. per cent. The total phosphorus content of the blood depends for its amount on (a) the relative proportion between the red blood corpuscles and the plasma, (b) the total phosphorus content of the plasma portion, and (c) the total phosphorus content of the red blood corpuscles portion.

The average total phosphorus content of the blood plasma was 13·89 mgrm. per cent., i.e., 5·8 per cent. above the normal average. In the individual cases, however, it was found to vary considerably in amount per cent. during the disease. It showed a tendency to be lowest at the commencement of the disease, then rose appreciably during the disease, and returned to the limits of normality on complete recovery of the patient. These changes were especially marked in Cases 1 and 2.

The average total phosphorus content of the red blood cells was calculated to be 92·8 mgrm. per 100 c.cm., i.e., 2·4 per cent. below the normal average. In the individual cases of acute nephritis, however, the total phosphorus content was found very much increased in amount per cent. of the corpuscles

CHART IV.

Relationship between the lipin phosphorus of plasma and calcium of blood serum in nephritis.



at the onset of the illness, then it decreased with marked fluctuation during the disease, and, on recovery, it returned to within the limits of normality.

Calcium content of the blood serum in nephritis.—Marriott and Howland[2], Halversan and his co-workers[13], de Wesselow[8], Briggs[7], and Schmitz and his co-workers[14] reported, in turn, that the calcium content of blood serum in nephritis was often diminished in amount per cent.

Determination of the calcium content in 20 different samples of blood serum from nephritic children was carried out; and there was a slight tendency for the calcium to decrease in amount per cent., the lowest value recorded being 8·07 mgrm. per cent.

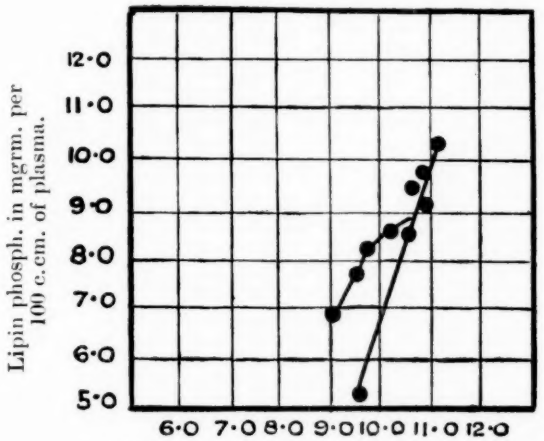
In the individual cases in which the calcium of blood serum was determined on several occasions during the course of the disease, no apparent

relationship between the free phosphorus of plasma and calcium content of the blood serum could be elicited. Binger[15] and Tisdall[16] reported a fall in calcium concentration of blood serum following the injection of phosphoric acid and its salts, but neither of them assigned this reduction in calcium to the accumulation of the inorganic phosphates in the blood serum.

On the other hand, the results showed some evidence in support of a relationship existing between the lipin phosphorus content of the blood plasma and the calcium content of blood serum in nephritis, which can be seen from Chart IV. This inter-relation was even more evident in the individual cases in which both the lipin phosphorus and calcium content were done simultaneously on several occasions during the disease. Both the lipin phosphorus and calcium either increased or decreased in amount per cent. at the same time and proportionately, i.e., the smaller the amount of one the smaller the amount of the other and vice versa, which can be seen from Chart V. The ratio, however, appeared to be different for each individual case.

CHART V.

Relationship between lipin phosphorus of plasma and calcium of serum in two cases of acute nephritis.



Summary.

(1) The free phosphorus of the blood in nephritis tended to rise above the normal level during the disease, and returned to the normal limits on recovery. The proportionate relationship between the free phosphorus of plasma and the red blood corpuscles was often disturbed during the disease.

(2) The increase in the free phosphorus and in the non-protein nitrogen of the blood frequently, but not invariably, occurred simultaneously.

(3) The percentage content of ester phosphorus of the blood showed a tendency to decrease.

(4) The percentage content of ester phosphorus of the blood plasma showed a tendency to increase.

(5) The ester phosphorus of the red blood corpuscles, or the so-called phosphorus index of blood, in nephritis showed much greater variation than in the normal. It was very high at the onset of nephritis.

(6) The percentage content of the lipin phosphorus of the blood, red blood corpuscles, and plasma showed appreciable variation during the disease.

(7) There was evidence of a relationship between the lipin and ester phosphorus compounds of the red blood corpuscles. Both of them showed a tendency either to fall or rise at the same time.

(8) The percentage content of the calcium of blood serum showed a tendency to be slightly diminished.

(9) There was evidence of a definite relationship between the lipin phosphorus of the blood plasma and the calcium content of the serum in nephritis.

PART III—DIABETES MELLITUS.

It seems clear that the phosphorus compounds of the blood are intimately associated with the metabolism of carbohydrates. Thus, it is well known that the concentration of the inorganic phosphates falls appreciably after a meal, and remains below the fasting level for several hours.

Wigglesworth and his co-workers[1] showed that the injections of insulin caused in rabbits a rapid fall in the inorganic phosphates of the blood, and Bollinger and Hartman[2] found that the fall was accompanied by a parallel diminution in the excretion of the inorganic phosphates in the urine. Harrop and Benedict[3] similarly found that, after administration of insulin and glucose, there was a decrease in the inorganic phosphates of blood; an increase in the inorganic phosphates of muscle, and a diminished excretion of the inorganic phosphates in the urine.

Bloor[4], and later Byrom[5] showed that the lipoids of the blood were markedly increased in severe diabetes mellitus but normal in the milder types. Friedlander and Rosenthal[6] reported that the intravenous injection of alkaline sodium phosphate caused in the diabetic a fall in the glucose concentration of the blood lasting for several hours while no change was observed in the percentage content of blood glucose in normal controls under the same conditions. They inferred from these observations that, as the respiratory quotient remained unaltered, synthesis of hexose-phosphate had occurred somewhere in the body.

The present study was undertaken to throw light on the distribution and partition of the phosphorus compounds and calcium of the blood in diabetes mellitus. The subjects of the study were four diabetic children (J. L. aged 5 years, J. B. 10 years, J. McK. 8 years, and A. G. 10 years). In three of the patients an attempt was made to determine the effect of treatment on the phosphorus content and distribution. Results are given in Table 3 (pp. 204-5).

Discussion.

Inorganic or free phosphorus.—The average of free phosphorus of the whole blood in 11 estimations of 4 diabetic children was found to be 15 per cent. below the normal average value. Only in 2 out of 11 estimations did the free phosphorus reach the normal level, and both these observations were made on

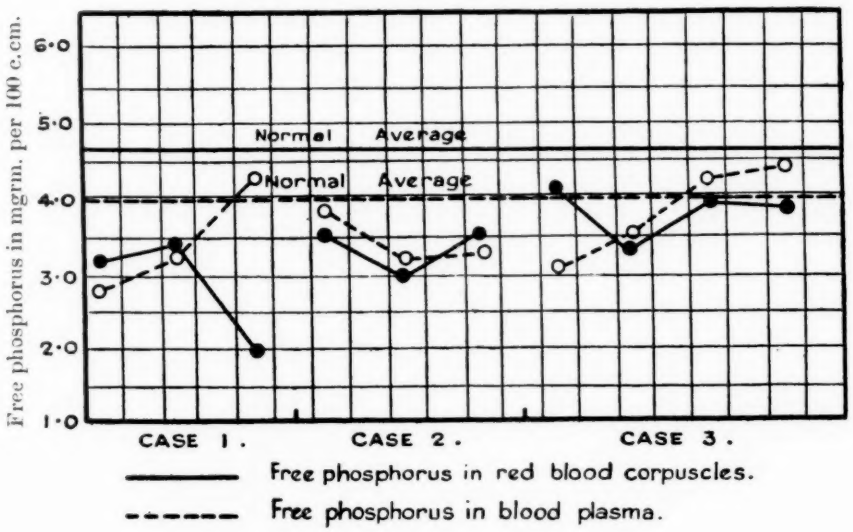
the same subject during the period in which the condition was well controlled by diet and insulin.

In 2 out of 3 cases the free phosphorus of the whole blood gradually rose towards the normal level as the metabolic disturbance was righted by means of careful dieting and insulin therapy. This distinct fall in the free phosphorus of the whole blood in diabetic children is not in accord with the findings for adults published by Byrom, who reported that there was no change in the concentration of the free phosphorus of the blood in diabetic adults until coma supervened when the value rose considerably.

The average free phosphorus of the blood plasma, although appreciably less than normal, was found to be greater than the free phosphorus of the whole blood. This is the reverse of the normal relationship existing between the free phosphorus of the whole blood, and blood plasma.

CHART VI.

Free phosphorus of the blood plasma and red blood corpuscles in three cases of diabetes mellitus.



The free phosphorus of the red blood corpuscles showed the most marked change. The average value was only 3·44 mgrm. per cent., i.e., 25·7 per cent. below the normal average. The lowest value recorded was 1·9. This poverty of the corpuscles in the free phosphorus was very striking, because not only did it exist in comparison to that of the corpuscles of normal children, but also in relation to amount of the free phosphorus in the whole blood, and plasma of diabetic children as can be seen from Chart VI.

Ester phosphorus compounds.—The average ester phosphorus of the whole blood was found to be slightly below the average for normal children. In the individual cases it showed a tendency to fall slightly in percentage as the condition improved.

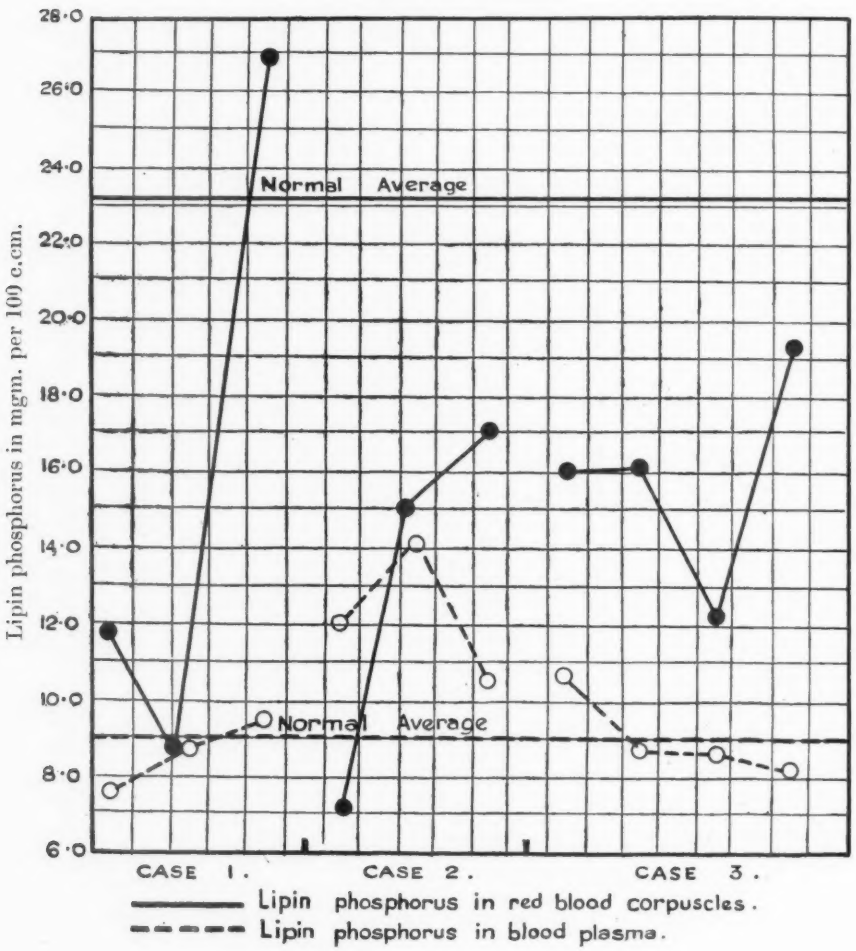
The average ester phosphorus of the red blood corpuscles or the so-called phosphoric index of the blood was found to be 61·3 mgrm. per cent., i.e., 8·8

mgrm. per cent. below the normal average. This confirmed the results of Byrom, who found a definite fall in the ester phosphorus of the corpuscles in diabetic patients being most marked in the coma stage when it was less than half of the normal.

The diminution in the ester phosphorus of the corpuscles in diabetic patients has not been explained satisfactorily, and different factors may play a part in its causation :—

CHART VII.

Lipin phosphorus of the red blood corpuscles and blood plasma in three cases of diabetes mellitus.



(1) It might be accounted for by the polyuria of diabetes mellitus, by which means an excessive amount of the free phosphorus is excreted by the kidney as a waste product, the ester phosphorus of the corpuscles being drawn upon by the process of hydrolysis to meet the existing deficit. That an excessive urinary excretion of phosphorus does take place in diabetes is indicated by the work of Ford from this laboratory*. In diabetic coma, however, there is

*These results have not been yet published.

often scanty secretion of urine or even anuria, although Byrom reported very low figures for the ester phosphorus of the corpuscles in such a condition. Further, that the polyuria per se is not the cause of the low value is also indicated by the high values for corpuscle-ester-phosphorus in the polyuria of chronic nephritis and diabetes insipidus as reported by Byrom and Kay[7].

(2) Acidosis has been suggested as a possible cause. Kay[8] recorded a fall in the ester phosphorus content of the red blood corpuscles in severe acidosis produced in a normal subject by the ingestion of ammonium chloride. Martland[9] found that lowering of the pH of the blood tended to increase the hydrolysis of the ester phosphorus while an increase of the pH favoured synthesis. In the present series of cases there was no clinical or biochemical evidence of acidosis.

(3) There has also to be considered the possibility that insulin is an important factor in the synthesis of the ester phosphorus of the corpuscles from the free phosphorus of the plasma. The present findings lend no support to this view, for in no case was there recorded any increase in amount of the ester phosphorus of red blood corpuscles after the institution of insulin treatment. On the contrary Case 3 showed a distinct fall in the ester phosphorus of corpuscles as the condition became controlled by diet and insulin.

Lipin phosphorus compounds.—The average lipin phosphorus of the whole blood was found to be 15 per cent. below normal. This fall in Case 2 is especially noteworthy as the blood from this patient was lipæmic on every occasion on which it was submitted to analysis. The fall was entirely at the expense of the cellular portion of the whole blood. During treatment the lipin phosphorus showed a tendency to return to normal limits.

The average lipin phosphorus of the red blood corpuscles was found to be 14·93 mgrm. per cent., i.e., 35·8 below the normal level. The lowest value recorded was 7·35 as can be seen from Chart VII. These results not only fail to confirm the findings of Bloor and Byrom, each of whom found independently that lipoids were increased in severe diabetes mellitus, and normal in mild cases, but they show a marked poverty of the red blood corpuscles in lipin phosphorus. The fact that in 3 out of our 4 cases the diabetic condition was of a mild character only emphasizes this difference.

Total phosphorus content.—The average total phosphorus of the blood was found to be 36·34 mgrm. per cent., and this is 9·3 per cent. below the normal. In individual cases there was an appreciable variation in amount of the total phosphorus on different occasions Thus, the samples of blood in Case 3 were analysed on four different occasions during the disease, and the total phosphorus of the blood varied from 34·28 to 41·6 mgrm. per cent.

The average phosphorus content of the blood plasma was found to be slightly above the normal level, and this was accounted for by the fact that there was lipæmia in one of the cases throughout.

Calcium content of the blood serum.—The calcium content of blood serum in diabetic patients was found to be within the limits of normality. The lowest figure reported was 9·1 mgrm. per cent., and the highest was 12·3 mgrm. per cent. of the blood serum.

Summary.

(1) The free phosphorus of the blood in diabetes mellitus is reduced. The reduction is much more marked in the corpuscles than in the plasma, so much so that the plasma content exceeds that of the red blood corpuscles, a state of affairs which is the reverse of normal. The free phosphorus both in corpuscles and plasma rises as the diabetic condition improves under treatment.

(2) The ester phosphorus of the red blood corpuscles is slightly decreased in amount.

(3) The lipin phosphorus of the corpuscles is markedly diminished in amount. During treatment it showed a tendency to a gradual return to within normal limits.

(4) The total phosphorus content of the blood is slightly diminished in amount.

(5) The calcium content of the blood serum keeps within the normal limits.

PART IV—INFANTILE TETANY AND IDIOPATHIC CONVULSIONS.

The close association of tetany with rickets, and the fact that the metabolism of phosphorus is disturbed in both conditions suggested the advisability of investigating the distribution of the various phosphorus compounds in these conditions. Five patients with signs of active tetany and rickets were studied, together with two infants suffering idiopathic convulsions of infancy. The results are given in Table 4 (pp. 204-5).

Inorganic or free phosphorus.—Numerous investigations have been carried out on the inorganic or free phosphorus of the blood in infantile tetany (Howland and Marriott[1], Kramer and his co-workers[2], Hess and his co-workers[3], Hoag[4], Scott and Usher[5], and Marples and Crump[6]), and the results indicated that in a certain number of cases the percentage content of free phosphorus is raised.

In 3 out of 5 cases of infantile tetany, reported in this paper, the free phosphorus of the whole blood, plasma, and the red blood corpuscles was found to be raised by 30–40 per cent. above the normal average value, and in the other two cases it was within the limits of normality.

The free phosphorus of the whole blood, plasma, and the corpuscles in 2 cases of idiopathic convulsions was also found to be markedly increased. In one case the value was 80 per cent. above the normal level. Young infants give rather higher values for free phosphorus than do older children, but, in this instance, the values were too high to be accounted for satisfactorily by the factor of age alone. There was nothing to suggest the possibility of defective renal efficiency and no other cause can be suggested for the condition.

Ester phosphorus compounds.—The ester phosphorus of the whole blood in 4 out of 5 cases of infantile tetany was decreased in amount by 2·5 to 12·5 per cent. It was also decreased in the 2 cases of idiopathic convulsions.

The ester phosphorus of the blood plasma, though very small in amount, in 3 cases of infantile tetany was below the normal average, and in the other 2 cases it was above the normal average. The ester phosphorus of the blood plasma in 2 cases of idiopathic convulsions showed a tendency to be above the normal average.

The ester phosphorus of the red blood corpuscles both in the infantile tetany cases and idiopathic convulsions cases was found to be within the normal limits.

Lipin phosphorus compounds.—The blood both of cases of infantile tetany and idiopathic convulsions showed a tendency to be 15 to 40 per cent. poorer in the lipin phosphorus than the blood of normal children.

The lipin phosphorus of the blood plasma in 4 out of 5 cases of infantile tetany and in both cases of idiopathic convulsions was found to be diminished in amount by 30 per cent.

The lipin phosphorus of the red blood corpuscles in 4 out of 5 cases of infantile tetany was below the normal average, whereas the lipin phosphorus of the corpuscles of the 2 cases of idiopathic convulsions was within the limits of normality.

Total phosphorus content.—The average total phosphorus content of the blood in cases of infantile tetany was found to be 36·23 mgrm. per cent., i.e., 9·6 per cent. below the normal level. The average total phosphorus of the blood in 2 cases of idiopathic convulsions was 13 per cent. below the normal level.

The average total phosphorus of the blood plasma both in infantile tetany and idiopathic convulsions was found to be slightly below the normal average.

The total phosphorus content of the red blood corpuscles in cases of infantile tetany was found to be below the normal average whereas within the limits of normality in cases of idiopathic convulsions.

Calcium content of the blood serum.—The calcium content of the blood serum in cases of infantile tetany was found markedly reduced in amount per cent. The highest value recorded was 8·1 mgrm. per cent. The values for all the other cases were below 6·0 mgrm. per cent.

Summary.

(1) The free phosphorus of the blood in 3 out of 5 cases of infantile tetany and both cases of idiopathic convulsions showed a tendency to rise above the normal level.

(2) The ester phosphorus of the blood in both conditions showed a tendency to diminish in amount. The ester phosphorus of the blood plasma was found to vary in amount in tetany, and to increase in convulsions.

(3) The lipin phosphorus of the blood, and blood plasma was diminished in amount in both conditions. The lipin phosphorus of the corpuscles diminished in amount in tetany, and remained normal in idiopathic convulsions.

(4) The total phosphorus content of the blood, and blood plasma was slightly decreased in both conditions.

The total phosphorus of the corpuscles was diminished in amount in tetany but it was within normal limits in idiopathic convulsions.

PART V—MISCELLANEOUS GROUP OF DISEASES.

Comparatively few data are available concerning the complete partition of the phosphorus compounds of the blood in pathological conditions other than those already mentioned above.

McGlusky[1], Roller[2], and Byron and Kay[3] studied independently the partition of phosphorus compounds of the blood in certain diseases, and they reported, though inconclusive, variations.

In this paper are detailed the results concerning the partition of phosphorus compounds of the blood in a group of patients suffering from blood disease and a variety of other conditions (rickets, albuminuria, dwarfism and ununited fracture). The results are given in Table 5 (pp. 206-7).

Though the results for any particular disease are too scanty to warrant any definite conclusions yet they indicate some interesting changes in the deviations from the normal.

Inorganic or free phosphorus.—The free phosphorus of the blood was found to be within normal limits in secondary anæmia and lymphadenoma. In the other conditions it was either above or below the normal level. The relationship between the free phosphorus of the blood, plasma and the red blood corpuscles was found to be upset at the expense of the latter in purpura simplex, rickets, albuminuria and lymphadenoma.

Ester phosphorus compounds.—The ester phosphorus of the blood was below the normal level in all the conditions studied except ununited fracture and dwarfism where it was slightly above the normal average value.

The ester phosphorus of the red blood corpuscles was within the normal limits in purpura simplex, ununited fracture, rickets, and dwarfism. It was below the normal in albuminuria and lymphadenoma, but 17·0 per cent. above the normal in secondary anæmia. These findings for anæmia are in agreement with the findings of Byrom and Kay, and also with what one might expect if there were an increased proportion of the young cells in blood whose ester phosphorus content is generally admitted to be slightly greater than in the normal.

Lipin phosphorus compounds.—The lipin phosphorus of the blood was invariably diminished to some extent in all the conditions.

The lipin phosphorus of the blood plasma showed a tendency to decrease in amount in all the conditions except albuminuria where it was actually above the normal.

The lipin phosphorus of the red blood corpuscles showed a marked tendency to fall in amount in all the conditions except ununited fracture, where it was found markedly increased. In the case of albuminuria the lipin phosphorus of the corpuscles was less than half of the normal average.

The lipin phosphorus of the corpuscles in secondary anæmia was found to be about 30·0 per cent. below the normal. Bloor and Macpherson[4] found that the lipoid composition of the corpuscles in anæmia was normal in almost all the cases. Further, Bloor[5] studied rabbits in which lipæmia was produced by the acute experimental anæmia through hæmorrhage, and he showed that of all the phosphoric acid compounds of the blood the lipoid phosphorus was most markedly affected by the anæmia and subsequent lipæmia. Values up

to 5 times the normal were found in the blood plasma, and 2 or more times the normal in the corpuscles. He concluded that the only phosphorus compound which was notably higher in the newly formed red blood corpuscles than in the older ones was the lipoid phosphorus. The results for the lipin phosphorus of our cases of secondary anæmia showed a definite tendency to be slightly diminished in the blood plasma, and markedly so in the red blood corpuscles. This difference might be due to the fact that his results were obtained from rabbits after an experimental anæmia followed by lipæmia, whereas our results were obtained from the blood of patients suffering from secondary anæmia with no evidence of lipæmia.

Byrom and Kay[3] showed that in individual cases of secondary anæmia the phosphorus partition varied, but the average figures indicated that, on the whole, the changes were due merely to alteration in the relative proportion of the corpuscles to the plasma in blood, and were not due to any quantitative change in the nature of their phosphorus compounds. As they appear to have estimated only the phosphorus compounds of the ' whole ' blood, it was very easy to arrive at somewhat deceptive conclusions. Thus, as the relative diminution of the cellular portion of the blood in secondary anæmia is seldom very marked, and as the blood plasma contains an appreciable amount of the lipin phosphorus, there cannot be expected more than a slight diminution in the lipin phosphorus per 100 c.cm. of the whole blood. If, however, this slight diminution is directly at the expense of the corpuscles, and the latter are relatively diminished, it is evident that the fall in the percentage of lipin phosphorus of the corpuscles will be much greater than that of the whole blood, and this our results confirm.

The effect of pituitary extract on the partition of phosphorus compounds of the blood in a case of dwarfism.—This case was a girl aged 9½ years, who had stopped growing normally at the age of 5 years. Her actual height was 102·5 cm., the normal for her age being 128·5 cm. Her actual weight was 16·92 kgrm., and the expected weight for her age is 27·5 kgrm. The condition was diagnosed as one of pituitary dwarfism.

A sample of her blood having been analysed for the phosphorus compounds, she was given pituitary extract for two months, at the end of which the blood was re-analysed, the results compared, and the difference between the two worked out in percentages. The results are given in Table 6 (pp. 206-7).

PART VI—GENERAL DISCUSSION OF RESULTS.

One of the most significant observations forcing itself into prominence from all the present investigations on phosphorus partition of the blood in disease, is that the phosphorus compounds of the blood in disease show a tendency to suffer a redistribution. These changes in distribution vary greatly in different diseases. In no disease was there found any tendency for an increase of total phosphorus content of the blood above the normal average value. In the individual phosphorus compounds of the blood, blood plasma, and red blood corpuscles, there were changes in either direction, i.e.,

either increased or decreased. Of the free, ester, and lipin phosphorus fractions the ester phosphorus showed the greatest stability. In healthy children, it was shown that the ester phosphorus, as well as lipin phosphorus, of the red blood corpuscles were constant ingredients, but in disease the ester phosphorus fraction suffered less change than the lipin phosphorus fraction which invariably and markedly did suffer per unit volume. Price-Jones[6] demonstrated that in disease the red blood corpuscles were large, the average volume of a cell, according to Haden[7], being 1·42 times greater than the normal average. Larger cells would indicate a smaller surface area per unit volume of cells, and a smaller total volume of the surface film with a relatively larger content of those constituents which do not occupy the surface. Thus, this would support the suggestion that the phosphoric esters were not on the surface of the cells but in the interior, which would be the opposite of the hæmoglobin as indicated by the experiments of Burker[8], and Emmons[9] who believed that the pigment was distributed superficially over the cells. Similarly Garter and Grendel[10] stated that the surface of the red cells was covered by a layer of the lipin molecules which was two molecules thick, and it would follow from this that the smaller the surface of the red cells the fewer the lipin molecules per unit volume. If this were true both of the ester phosphorus fraction and the lipin molecules, it would not be idle to suggest that (a) the ester phosphorus fraction, being inside the cells, would be less likely to be affected, for, within limits, the fewer the cells the greater their size, and they could thus accommodate relatively greater amounts of the phosphoric esters; (b) the amount of lipin phosphorus fraction would depend directly upon the sum total of the surface of the cells; and (c) the lipin phosphorus, being lodged on the surface, might further account for its lability, for it would be more likely than not that, under stress of disease, the superficial layers of the red blood corpuscles would be the first to bear its brunt.

General conclusions.

(1) In all the diseases studied marked changes in the partition of the phosphorus compounds of the blood were noted.

(2) The changes which took place were not identical in all the diseases, but the most frequent and marked changes related to the free and lipin phosphorus fractions.

(3) In no disease was there noted any accumulation in the phosphorus content of the blood, but merely a redistribution of the different phosphorus compounds. There was, however, noticed a tendency for the total phosphorus content of the blood to fall in amount during disease.

In conclusion, it is a pleasant duty to acknowledge my gratitude to Prof. Leonard Findlay for his criticism throughout. Further, I am greatly indebted to Dr. N. Morris for his invaluable advice in matters of biochemical analysis, constant encouragement, and assistance to select suitable cases for the study to Dr. S. B. Fleming for facilities for studying some of the cases; and to Dr. S. Graham for estimating the non-protein nitrogen of blood for me, and other assistance willingly given on innumerable occasions.

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(*References concluded on p.* 208)

EXPLANATION OF TABLES.

TABLES :—F.P.=Inorganic or free phosphorus; F.E.P.=Inorganic plus ester phosphorus; E.P.=Ester phosphorus; L.P.= lipin phosphorus; T.P.(C.) and (A.)= Total phosphorus by combustion and addition respectiveiy; Ca=Calcium; N.P.N.=Non-protein-nitrogen.

TABLE

PHOSPHORUS COMPOUNDS OF THE BLOOD

Case No.	Age years	Diagnosis	Whole blood					
			F.P.	F.E.P.	E.P.	L.P.	T.P.(C.)	T. .(A.)
1	8	Normal	3·89	23·58	20·69	13·7	36·7	37·28
2	12	Do.	4·4	29·2	24·8	13·9	43·24	43·1
3	11	Do.	4·1	31·4	27·3	12·9	45·1	44·3
4	11	Do.	4·6	30·3	26·7	14·1	43·3	44·4
5	8½	Do.	4·6	24·7	20·1	15·4	39·6	40·1
6	5	Do.	4·04	23·8	19·76	14·2	38·7	38·0
7	9	Do.	3·8	24·24	20·44	12·5	36·9	36·74
8	5½	Do.	4·11	25·5	21·39	12·7	38·5	38·3
9	12	Do.	3·9	24·3	20·4	14·8	39·9	39·1
10	4	Do.	4·11	26·6	22·49	13·2	40·1	39·8
Average	—	—	4·15	26·36	22·4	13·74	40·2	40·11
Highest	—	—	4·6	31·4	27·3	15·4	45·1	44·4
Lowest	—	—	3·8	23·58	19·76	12·5	36·7	36·74

TABLE

PHOSPHORUS COMPOUNDS OF THE BLOOD

Case No.	Age in years	Diagnosis	Whole Blood					
			F.P.	F.E.P.	E.P.	L.P.	T.P.(C.)	T.P.(A.)
—	—	Normal average	4·15	26·36	22·4	13·74	40·2	40·11
1	11	Acute nephritis with uræmia	3·34	25·97	22·63	12·82	38·46	38·78
			6·94	26·6	19·66	13·7	38·5	40·3
			5·15	26·4	21·25	14·1	41·1	40·5
			4·48	24·24	19·76	10·88	35·8	35·12
			4·11	25·3	21·19	13·8	39·9	39·1
2	6¾	Acute nephritis with uræmia	3·11	25·64	22·53	12·25	38·2	37·89
			4·08	—	—	—	—	—
			4·06	26·2	22·14	13·62	38·65	39·82
			3·7	23·8	20·1	11·57	35·1	35·37
3	5½	Acute nephritis	5·2	26·1	20·9	9·0	34·8	35·1
			3·74	21·73	17·99	12·62	34·26	34·35
			5·1	24·2	19·1	12·07	35·84	36·27
			4·2	22·7	18·5	11·2	33·85	33·9
			3·83	23·5	19·67	12·9	35·9	36·4
4	6½	Acute nephritis	5·1	24·3	19·2	12·07	35·7	36·37
			4·71	24·5	19·79	11·4	35·84	35·9
			4·1	24·2	20·1	13·1	37·56	37·3
5	9¾	Acute nephritis	5·8	26·1	20·3	13·28	39·87	39·38
			4·96	27·2	22·24	14·1	41·6	41·3
			4·1	26·8	22·7	13·5	40·49	40·3
6	8	Acute nephritis	4·96	26·3	21·34	13·18	40·79	40·1
7	3½	Acute nephritis	5·2	26·6	21·4	13·9	40·87	40·5
8	12¼	Acute nephritis	4·13	24·7	20·54	8·95	33·6	33·65
9	12	Chronic nephritis	4·5	27·21	22·71	10·3	37·23	37·51
10	11½	Subacute nephritis ...	4·5	26·6	22·1	13·9	40·16	40·5

1.

IN NORMAL CHILDREN. (mgrm. per cent.)

Plasma					Corpuscles				Hæma-tocrit R.B.C.%	Ca in serum	R.B.C. in millions
F.P.	F.E.P.	E.P.	L.P.	T.P.	F.P.	L.P.	E.P.	T.P.			
3·53	4·14	0·61	10·1	14·24	4·7	21·7	65·4	91·8	31·0	10·9	—
4·2	4·8	0·6	8·9	13·7	4·93	25·3	80·2	110·4	30·4	—	4·8
3·9	4·37	0·47	8·53	12·9	4·47	20·9	76·9	102·27	35·1	10·08	5·1
4·2	4·6	0·4	10·7	15·3	5·46	20·0	71·8	97·26	36·8	11·04	—
4·39	4·6	0·21	9·9	14·5	4·94	24·0	51·4	80·34	38·8	10·9	—
3·8	4·1	0·3	10·1	12·8	4·58	23·1	62·2	89·88	31·4	10·76	4·86
3·58	3·73	0·15	7·87	11·6	4·33	23·3	67·8	95·43	30·0	11·0	4·4
4·01	4·33	0·32	8·69	11·9	4·35	22·6	73·7	100·65	28·7	10·7	4·51
3·7	4·05	0·35	6·61	10·66	4·23	28·7	54·8	87·73	36·8	11·1	—
4·0	4·4	0·4	9·2	13·6	4·33	23·0	68·3	95·63	32·5	10·1	—
3·93	4·31	0·38	9·06	13·12	4·63	23·26	67·25	95·13	33·1	10·73	—
4·39	4·8	0·61	10·7	15·3	5·46	28·7	80·2	110·4	38·8	11·1	—
3·53	3·73	0·15	6·61	10·66	4·23	20·0	51·4	80·34	28·7	10·08	—

2.

IN NEPHRITIS. (mgrm. per 100 c.cm.)

Plasma					Corpuscles				Hæma-tocrit R.B.C.%	Ca in serum mgrm. %	Blood N.P.N. mgrm. %
F.P.	F.E.P.	E.P.	L.P.	T.P.	F.P.	L.P.	E.P.	T.P.			
3·93	4·31	0·38	9·06	13·12	4·63	23·26	67·25	95·13	33·15	10·73	—
3·13	5·3	2·17	5·1	10·4	3·8	31·7	72·7	108·2	29·0	9·72	32·1
6·94	7·5	0·6	9·54	17·04	6·95	21·7	56·3	85·0	34·2	10·9	54·5
4·9	5·5	0·6	10·2	15·7	5·7	23·65	71·8	101·2	29·0	11·1	57·1
4·59	5·0	0·41	8·57	13·16	4·25	15·5	58·3	78·05	33·4	10·7	—
4·4	4·76	0·36	9·64	13·4	3·5	23·9	61·8	89·2	33·9	10·9	33·3
3·68	4·07	0·39	8·65	12·72	3·2	23·29	90·4	116·89	24·6	—	84·4
—	—	—	—	—	—	—	—	—	—	—	—
3·95	4·58	0·63	11·72	16·3	4·4	19·6	90·2	114·2	24·0	—	34·0
3·69	4·1	0·41	9·78	13·88	3·74	17·1	81·4	102·24	24·3	—	—
4·98	5·5	0·52	6·99	12·5	5·87	15·1	83·7	104·67	24·5	9·04	39·1
3·77	4·03	0·26	9·12	13·15	3·7	20·9	55·1	78·8	32·3	10·9	—
5·38	6·15	0·77	8·06	14·08	4·4	22·3	65·7	92·4	28·2	9·76	—
4·34	4·7	0·36	7·7	12·4	3·9	18·7	57·4	80·0	31·8	9·56	—
3·89	4·2	0·31	8·5	12·7	3·69	22·8	63·6	90·1	30·6	10·2	—
4·56	5·08	0·52	8·22	13·3	6·66	23·46	74·0	104·12	25·6	10·08	62·3
4·59	4·8	0·21	7·68	12·66	4·96	19·3	61·7	85·96	31·8	9·6	—
3·92	4·35	0·43	8·9	13·15	4·58	24·07	71·4	100·05	27·7	—	44·4
5·73	6·05	0·32	8·41	14·46	5·9	22·2	57·0	85·1	35·2	9·84	43·5
4·8	5·42	0·62	9·28	14·7	5·28	23·59	64·39	93·26	33·9	9·3	31·6
3·93	4·4	0·43	9·27	13·67	4·5	22·0	67·9	94·4	33·0	10·7	30·1
4·73	4·99	0·26	9·16	14·15	5·33	20·0	57·0	82·33	37·1	9·26	—
5·0	5·4	0·4	10·1	15·5	5·8	23·0	72·0	100·8	29·3	8·8	71·8
3·55	3·78	0·23	6·02	9·8	5·1	14·2	56·9	76·2	35·8	8·07	—
4·28	4·64	0·36	10·05	14·69	4·9	10·7	63·8	79·4	35·2	9·86	—
4·4	5·03	0·63	12·27	17·3	4·7	17·8	74·4	96·9	29·1	9·6	—

TABLE

PHOSPHORUS COMPOUNDS OF THE
(mgrm. per

Case No.	Age in years	Diagnosis	Whole blood					
			F.P.	F.E.P.	E.P.	L.P.	T.P.(C.)	T.P.(A.)
—	—	Normal average	4·15	26·36	22·4	13·74	40·2	40·11
1	4	Diabetes mellitus	3·0	24·4	21·4	9·1	34·0	33·5
			3·3	27·4	24·1	8·9	37·6	36·3
			3·5	22·2	18·7	14·9	37·4	37·1
2	10	Diabetes mellitus	3·8	24·0	20·2	10·4	34·2	34·4
			3·17	25·3	22·13	14·8	39·75	40·1
			3·4	21·53	18·13	12·98	34·72	34·51
3	8	Diabetes mellitus	3·48	28·7	25·22	12·9	41·4	41·6
			3·49	25·83	22·34	11·26	37·45	37·09
			4·11	24·06	19·95	10·22	34·52	34·28
			4·2	26·7	22·5	12·36	39·3	39·06
4	10	Diabetes mellitus	3·54	23·46	19·92	8·4	32·05	31·86

TABLE

PHOSPHORUS COMPOUNDS OF THE BLOOD IN
(mgrm. per

Case No.	Age in years	Diagnosis	Whole Blood					
			F.P.	F.E.P.	E.P.	L.P.	T.P.(C.)	T.P.(A.)
		Normal average	4·15	26·36	22·4	13·74	40·2	40·11
1	$1\frac{1}{12}$	Infantile tetany	5·5	22·9	17·35	8·0	31·2	30·9
2	$4\frac{1}{6}$	Do.	3·5	23·4	19·9	10·4	33·4	33·8
3	$1\frac{1}{2}$	Do.	4·04	25·2	21·16	11·7	37·4	36·9
4	$\frac{2}{3}$	Do.	5·74	27·1	21·36	10·4	36·7	37·5
5	$1\frac{5}{12}$	Do.	6·1	33·4	27·3	9·26	42·73	42·66
		Average	4·97	26·4	21·41	9·95	36·28	36·23
7	4 weeks	Idiopathic convulsions ...	6·49	25·3	18·81	11·41	36·7	36·76
8	5 weeks	Do.	5·37	23·1	17·73	9·8	33·3	32·9

3.

BLOOD IN DIABETES MELLITUS.

100 c.cm.)

Plasma					Corpuscles				Hæma-tocrit R.B.C. %	Ca in serum mgrm. %
F.P.	F.E.P.	E.P.	L.P.	T.P.	F.P.	L.P.	E.P.	T.P.		
3·93	4·31	0·38	9·06	13·12	4·63	23·26	67·25	95·13	33·15	10·73
2·85	5·56	0·71	7·7	11·26	3·3	11·7	60·1	75·1	34·8	9·9
3·25	4·02	0·77	8·88	12·9	3·4	8·9	63·8	76·1	37·0	11·2
4·2	4·29	0·09	9·61	13·9	1·96	26·89	60·9	89·75	30·6	9·1
3·9	4·1	0·2	12·0	16·1	3·63	7·35	58·3	69·28	34·4	10·3
3·22	3·68	0·46	14·52	18·2	3·0	15·3	63·5	81·8	34·5	10·1
3·28	3·6	0·32	10·88	14·48	3·63	17·24	54·3	75·17	33·0	10·8
3·15	3·65	0·5	11·25	14·9	4·15	16·2	75·4	95·75	33·0	12·3
3·51	3·8	0·29	8·85	12·65	3·4	16·4	69·4	89·2	31·9	10·8
4·22	4·54	0·32	8·96	13·5	3·9	12·5	55·4	71·8	35·6	11·2
4·4	4·75	0·35	8·35	13·1	3·85	19·3	61·37	84·52	36·3	11·0
3·48	3·98	0·5	5·86	9·85	3·65	12·5	51·8	67·95	37·8	10·47

4.

INFANTILE TETANY AND IDIOPATHIC CONVULSIONS.

100 c.cm.)

Plasma					Corpuscles				Hæma-tocrit R.B.C. %	Ca in serum mgrm. %
F.P.	F.E.P.	E.P.	L.P.	T.P.	F.P.	L.P.	E.P.	T.P.		
3·93	4·31	0·38	9·06	13·12	4·63	23·26	67·25	95·13	33·15	10·73
5·4	5·53	0·13	4·06	9·59	5·9	18·2	61·6	85·7	28·0	8·1
3·22	3·36	0·14	6·39	9·75	4·15	19·4	64·2	87·75	30·8	5·2
3·89	4·5	0·61	6·0	10·5	4·34	23·0	62·1	89·44	33·4	5·3
5·2	5·45	0·25	9·47	14·92	7·1	12·7	74·9	94·7	28·4	4·8
6·17	6·58	0·41	6·48	12·65	6·0	13·7	70·3	90·0	38·5	5·2
4·75	5·08	0·3	6·48	11·48	5·5	17·4	66·6	89·52	31·8	5·72
5·79	6·25	0·46	7·35	13·6	8·5	23·3	72·7	104·5	25·4	—
5·3	5·9	0·6	5·18	11·08	5·5	21·8	62·2	89·5	27·8	—

TABLE

PHOSPHORUS COMPOUNDS OF THE
(mgrm. per

Case No.	Age in years	Diagnosis	Whole blood					
			F.P.	F.E.P.	E.P.	L.P.	T.P.(C.)	T.P.(A.)
		Normal Average	4·15	26·36	22·4	13·74	40·2	40·11
1	12	Secondary anæmia	4·52	23·5	18·98	10·01	33·6	33·51
2	$6\frac{1}{2}$	Do.	3·98	23·6	19·62	10·3	34·2	33·9
3	8	Do.	4·1	25·3	21·2	11·2	36·17	36·5
4	$3\frac{1}{2}$	Purpura simplex	3·25	20·61	17·36	9·05	30·4	29·66
5	$6\frac{1}{2}$	Ununited fracture	6·1	29·2	23·1	13·2	43·8	42·4
6	$1\frac{5}{12}$	Rickets	3·21	23·84	20·63	12·07	36·43	35·91
7	$5\frac{1}{2}$	Albuminuria...	4·87	25·9	21·3	10·22	36·23	36·12
8	8	Lymphadenoma	4·06	23·89	19·83	11·74	36·13	35·63
9	$9\frac{1}{2}$	Dwarfism	4·36	29·2	24·84	9·8	39·13	39·0

TABLE

THE EFFECT OF PITUITARY EXTRACT ON THE PARTITION OF
(mgrm. per

	Whole blood					
	F.P.	F.E.P.	E.P.	L.P.	T.P.(C.)	T.P.(A.)
Before treatment	4·36	29·2	24·84	9·8	39·13	39·0
Two months after treatment	3·98	23·6	19·62	10·3	34·2	33·9
Difference in percentage	—8·7%	—19%	—21%	+5·1%	—12·6%	—13%

TABLES :—F.P.=Inorganic or free phosphorus; F.E.P.=Free plus ester phosphorus; E.P.=Ester respectively; Ca=Calcium. N.P.N.=Non-protein-nitrogen.

5.

BLOOD IN MISCELLANEOUS DISEASES.
100 c.cm.)

Plasma					Corpuscles				Hæmo-tocrit R.B.C. %	Ca in serum mgrm. %
F.P.	F.E.P.	E.P.	L.P.	T.P.	F.P.	L.P.	E.P.	T.P.		
3·93	4·31	0·38	9·06	13·12	4·63	23·26	67·25	95·13	33·15	10·73
4·3	4·45	0·15	8·15	12·6	5·2	16·5	81·3	103·0	23·2	10·8
3·8	4·1	0·3	8·4	12·5	4·6	16·1	79·5	100·2	24·4	10·9
3·8	4·2	0·4	9·1	13·1	4·87	16·6	74·9	96·37	27·9	9·12
3·32	3·7	0·38	7·2	10·52	3·07	13·7	60·3	77·1	28·3	11·06
5·13	8·2	3·07	5·4	13·6	7·9	28·1	61·1	97·1	34·5	11·1
3·32	3·52	0·2	8·55	12·07	2·9	19·6	64·6	87·1	31·7	8·14
5·57	6·06	0·49	9·81	15·87	3·6	10·9	57·8	71·6	36·3	—
4·2	4·56	0·36	6·08	10·69	3·79	22·6	57·1	83·49	34·3	9·8
4·03	4·7	0·67	7·76	12·46	5·0	13·9	73·4	92·3	33·2	9·91

6.

PHOSPHORUS COMPOUNDS OF THE BLOOD IN A CASE OF DWARFISM.
100 c.cm.)

Plasma					Corpuscles				Hæma-tocrit R.B.C. %	Ca in serum mgrm. %
F.P.	F.E.P.	E.P.	L.P.	T.P.	F.P.	L.P.	E.P.	T.P.		
4·03	4·7	0·67	7·76	12·46	5·0	13·9	73·4	92·3	33·2	9·91
3·8	4·1	0·3	8·4	12·5	4·5	16·1	79·4	100·0	24·4	10·9
—5·7%	—12·8%	—55%	+8·2%	0	—10%	+15·8%	+8·1%	+8·3%	—26·5%	+10%

phosphorus; L.P.=Lipin phosphorus; T.P.(C.) and T.P.(A.)=Total phosphorus by combustion and addition

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